



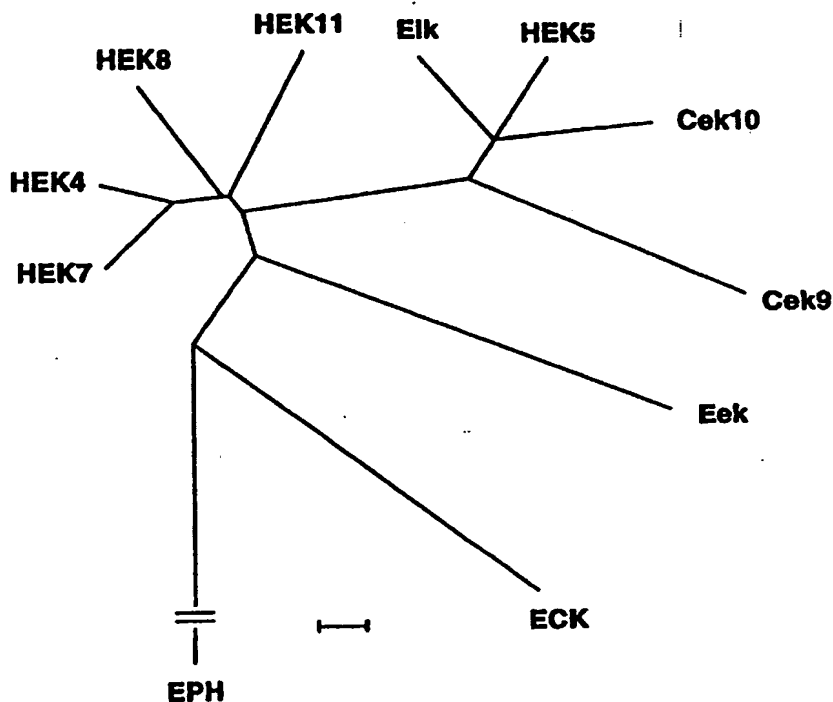
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/12, C07K 14/71, 16/28, A61K 38/17, 39/395, C12N 15/62, G01N 33/566		A1	(11) International Publication Number: WO 95/28484
			(43) International Publication Date: 26 October 1995 (26.10.95)
(21) International Application Number: PCT/US95/04681		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).	
(22) International Filing Date: 14 April 1995 (14.04.95)			
(30) Priority Data: 08/229,509 15 April 1994 (15.04.94) US			
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(54) Title: HEK5, HEK7, HEK8, HEK11, NEW EPH-LIKE RECEPTOR PROTEIN TYROSINE KINASES

(57) Abstract

Four novel members of the EPH sub-family of receptor protein tyrosine kinases are disclosed. Nucleic acid sequences encoding receptor proteins, recombinant plasmids and host cells for expression, and methods of producing and using such receptors are also disclosed.



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HEK5, HEK7, HEK8, HEK11, new EPH-like receptor protein tyrosine kinases

Field of the Invention

5 The invention relates generally to receptor protein tyrosine kinases (PTKs) and particularly to novel Eph-like receptor PTKs, to fragments and analogs thereof, and to nucleic acids encoding same. The present invention also relates to methods of producing
10 and using such receptors.

Background of the Invention

 Receptor PTKs are a structurally related
15 family of proteins that mediate the response of cells to extracellular signals (Ullrich et al. Cell 61, 203-212 (1990)). These receptors are characterized by three major functional domains: an intracellular region containing the sequences responsible for catalytic
20 activity, a single hydrophobic membrane-spanning domain, and a glycosylated extracellular region whose structure determines ligand binding specificity. Signal transduction is initiated by the binding of growth or differentiation factors to the extracellular domain of
25 their cognate receptors. Ligand binding facilitates dimerization of the receptor which can induce receptor autophosphorylation. Both soluble and membrane-associated protein ligands have been shown to function in this manner. This process is the initial step in a
30 cascade of interactions involving the phosphorylation of a variety of cytoplasmic substrates and culminating in a biological response by the cell. The best characterized response to tyrosine kinase receptor activation is cell
35 factors in vivo suggests that differentiation or cell

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survival might also be mediated by tyrosine kinase receptor/ligand interactions.

Receptor PTKs have been grouped into fairly
5 well-defined families on the basis of both sequence
homology and shared structural motifs. The amino acid
sequence of the portion of the intracellular domain
responsible for the catalytic activity is well conserved
among all tyrosine kinases and even more closely matched
10 within a receptor sub-family. Comparisons of this
portion of the amino acid sequence have been used to
construct phylogenetic trees depicting the relatedness
of family members to each other and to the tyrosine
kinases as a whole (Hanks and Quinn, Methods Enzymol.
15 200, 38-62 (1991)). This sequence conservation has also
been exploited in order to isolate new tyrosine kinases
using the polymerase chain reaction (PCR) (Wilks, Proc.
Natl. Acad. Sci. USA 86, 1603-1607 (1989)).
Oligonucleotides based on the highly conserved catalytic
20 domain of PTKs can be used as PCR primers to amplify
related sequences present in the template. These
fragments can then be used as probes for isolation of
the corresponding full-length receptor clones from cDNA
libraries. Anti-phosphotyrosine antibodies have also
25 been used to identify PTK cDNA clones in phage
expression libraries (Lindberg and Pasquale, Methods
Enzymol. 200, 557-564 (1991)). These strategies have
been used by a number of investigators to identify an
ever-increasing number of protein tyrosine kinase
30 receptors.

There are now 51 distinct PTK receptor genes
that have been published and divided into 14
sub-families. One such sub-family is the EPH-like
35 receptors. The prototype member, EPH, was isolated by
Hirai et.al. (Science 238, 1717-1720 (1987)) using low

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stringency hybridization to a probe derived from the viral oncogene v-fps. EPH-like receptors have been implicated in cell growth based in part on studies which show that overexpression of the gene in NIH3T3 cells causes focus formation in soft agar and tumors in nude mice (Maru et al. Oncogene 5, 199-204 (1990)). Other members of the EPH sub-family which have been identified include the following:

- ECK (Lindberg et al. Mol. Cell. Biol. 10, 6316-6324 (1990))
- Elk (Lhoták et al. Mol. Cell. Biol. 11, 2496-2502 (1991))
- Ceks 4, 5, 6, 7, 8, 9, and 10 (Pasquale, Cell Regulation 2, 523-534 (1991); Sajjadi et al. The New Biologist 3, 769-778 (1991); Sajjadi and Pasquale Oncogene 8, 1807-1813 (1993))
- HEK2 (Bohme et al. Oncogene 8, 2857-2862 (1993))
- Eek, Erk (Chan and Watt, Oncogene 6, 1057-1061 (1991))
- Ehk1, Ehk2 (Maisonpierre et al. Oncogene 8, 3277-3288 (1993))

Homologs for some of these receptors have been identified in other species (Wicks et al. Proc. Natl. Acad. Sci. USA 89, 1611-1615 (1992)); Gilardi-Hebenstreit et al. Oncogene 7, 2499-2506 (1992)). The expression patterns and developmental profiles of several family members suggest that these receptors and their ligands are important for the proliferation, differentiation and maintenance of a variety of tissues (Nieto et al. Development 116, 1137-1150 (1992)). Structurally, EPH sub-family members are characterized by an Ig-like loop, a cysteine rich region, and two fibronectin-type repeats in their extracellular domains. The amino acid sequences of the catalytic domains are

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more closely related to the SRC sub-family of cytoplasmic PTKs than to any of the receptor PTKs. Among the catalytic domains of receptor PTKs, the EPH sub-family is most similar in amino acid sequence to the epidermal growth factor receptor sub-family.

It is an object of the invention to identify novel receptors belonging to the EPH sub-family. A directed PCR approach has been used to identify five human EPH-like receptors from a human fetal brain cDNA library. These receptors are designated HEK4, HEK5, HEK7, HEK8, and HEK11. The relationship of these receptors to previously identified EPH-like receptors is as follows:

HEK4 is the human homolog of Cek4 (chicken) and Mek4 (mouse) and is identical to HEK (Boyd et al. J. Biol. Chem. 267, 3262-3267 (1992); Wicks et al., 1992) which was previously isolated from a human lymphoid tumor cell line.

HEK5 is the human homolog of Cek5, a full-length eph-like receptor clone from chicken. A portion of the HEK5 sequence was previously disclosed as ERK, a human clone encoding about sixty amino acids (Chan and Watt, 1991)

HEK7 is the human homolog of Cek7 isolated from chicken.

HEK8 is the human homolog of Cek8 a full-length clone from chicken and Sek, a full-length clone from mouse. (Nieto et al., 1992; Sajjadi et al., 1991)

HEK11 does not have a known non-human homolog. With the addition of the new members HEK5, HEK7, HEK8 and HEK11 and the report of a PCR fragment encoding an eph-like receptor (Lai & Lemke Neuron 6, 691-704 (1991)), a total of twelve distinct sequences that represent EPH-like receptors have been published, making it the largest known sub-family of PTKs.

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It is a further object of the invention to generate soluble EPH-like receptors and antibodies to EPH-like receptors. Soluble receptors and antibodies are useful for modulating EPH-like receptor activation.

5

Summary of the Invention

The present invention provides novel EPH-like receptor protein tyrosine kinases. More particularly, the invention provides isolated nucleic acids encoding four novel members of the sub-family of EPH-like receptor PTKs which are referred to collectively as HEKs (human-eph like kinases). Also encompassed are nucleic acids which hybridize under stringent conditions to EPH-like receptor nucleic acids. Expression vectors and host cells for the production of receptor polypeptides and methods of producing receptors are also provided.

Isolated polypeptides having amino acid sequences of EPH-like receptors are also provided, as are fragments and analogs thereof. Antibodies specifically binding the polypeptides of the invention are included. Also comprehended by the invention are methods of modulating the endogenous activity of an EPH-like receptor and methods for identifying receptor ligands.

25

Description of the Figures

Figure 1 shows the nucleotide and predicted amino acid sequence of the HEK5 receptor.

Figure 2 shows the nucleotide and predicted amino acid sequence of the HEK7 receptor..

Figure 3 shows the nucleotide and predicted amino acid sequence of the HEK8 receptor.

35

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Figure 4 shows the nucleotide and predicted amino acid sequence of the HEK11 receptor.

Figure 5 shows the comparison of the amino acid sequences of the human EPH receptor sub-family. The multiple sequence alignment was done using the LineUp program included in the Genetics Computer Group sequence analysis software package (Genetics Computer Group, (1991), Program Manual for the GCG Package, Version 7, April 1991, Madison, Wisconsin, USA 53711). Dots indicate spaces introduced in order to optimize alignment. The predicted transmembrane domains and signal sequences of each receptor are indicated by underlining and italics, respectively. Cysteine residues conserved throughout the sub-family are indicated with asterisks. Arrows indicate the tyrosine kinase catalytic domain. Amino acid sequences of EPH, ECK and HEK2 were taken from the appropriate literature references.

Figure 6 shows the molecular phylogeny of the EPH sub-family of receptor protein tyrosine kinases. Catalytic domain sequences were analyzed as described by Hanks and Quinn, 1991. The scale bar represents an arbitrary evolutionary difference unit. The EPH branch, which has been shown with a discontinuity for the sake of compactness, is 23.5 units in length.

Figures 7-11 show Northern blot analyses of the tissue distribution of the HEK receptors. Receptor cDNA probes, labeled with ^{32}P , were hybridized to either 2 μg of poly A⁺ RNA from human tissues (panel A, Clontech) or 10 μg of total RNA from rat tissues (panel B). Sizes of the transcripts were determined by comparison with RNA molecular weight markers (Bethesda Research Labs,

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Gaithersburg, MD). Figure 7, HEK4; Figure 8, HEK5; Figure 9, HEK7; Figure 10; HEK8; Figure 11; HEK 11.

Detailed Description of the Invention

5 The present invention relates to novel EPH-like receptor protein tyrosine kinases. More particularly, the invention relates to isolated nucleic acids encoding four novel members of the sub-family of EPH-like receptor PTKs. These four members are
10 designated herein as HEK (human eph-like kinases). Nucleic acids encoding HEK receptors were identified in a human fetal brain cDNA library using oligonucleotide probes to conserved regions of receptor PTKs and EPH-like receptor PTKs. The predicted amino acid sequences
15 of three HEK receptors had extensive homology in the catalytic domain to previously identified EPH-like receptors Cek5, Cek7 and Cek8 isolated from chicken and, accordingly, are designated HEK5, HEK7 and HEK8. The predicted amino acid sequence of the fourth HEK receptor
20 revealed that it was not a homolog of any previously identified EPH-like receptor. It is designated HEK11. It is understood that the term "HEKs" comprises HEK5, HEK7, HEK8 and HEK11 as well as analogs, variants, and mutants thereof which fall within the scope of the
25 invention.

The invention encompasses isolated nucleic acids selected from the group consisting of:

(a) the nucleic acids set forth in any of SEQ
30 ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, or SEQ ID NO: 16 and their complementary strands;

(b) a nucleic acid hybridizing to the coding regions of the nucleic acids in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, or SEQ ID NO: 16 under
35 stringent conditions; and

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(c) a nucleic acid of (b) which, but for the degeneracy of the genetic code, would hybridize to the coding regions of the nucleic acids in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, or SEQ ID NO: 16.

5 The nucleic acids of the invention preferably hybridize to HEK5, HEK7, HEK8, or HEK11 coding regions under conditions allowing up to about 5% nucleotide mismatch based upon observed nucleic acid identities among known human or nonhuman EPH-like receptors. An example of
10 such a condition is hybridization at 60° in 1M Na⁺ followed by washing at 60° in 0.2XSSC. Other hybridization conditions may be ascertained by one skilled in the art which allow base pairing with similar levels of mismatch.

15 In a preferred embodiment, the isolated nucleic acids encode polypeptides having the amino acid sequences of HEK5, HEK7, HEK8 or HEK11. A nucleic acid includes cDNA, genomic DNA, synthetic DNA or RNA. Nucleic acids of this invention may encode full-length
20 receptor polypeptides having an extracellular ligand-binding domain, a transmembrane domain, and a cytoplasmic domain, or may encode fragments such as extracellular domains which are produced in a soluble, secreted form. Nucleic acid constructs which produce
25 soluble HEK receptors are described in Example 3. Polypeptides and fragments encoded by the nucleic acids have at least one of the biological activities of an EPH-like receptor protein tyrosine kinase, such as the ability to bind ligand.

30 The invention also encompasses nucleic acids encoding chimeric proteins wherein said proteins comprise part of the amino acid sequence of a HEK receptor linked to an amino acid sequence from a
35 heterologous protein. One example of such a chimeric protein is an extracellular domain of a HEK receptor

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fused to a heterologous receptor cytoplasmic domain. Example 5 describes the construction and expression of a chimeric receptor comprising the HEK8 extracellular domain with the trkB cytoplasmic domain and a second
5 chimeric receptor comprising the HEK11 extracellular domain with the trkB cytoplasmic domain. HEK receptors may also be fused to other functional protein domains, such as an Ig domain which acts as an antibody recognition site.

10

The nucleic acids of the present invention may be linked to heterologous nucleic acids which provide expression of receptor PTKs. Such heterologous nucleic acids include biologically functional plasmids or viral
15 vectors which provide genetic elements for transcription, translation, amplification, secretion, etc. One example of an expression vector suitable for producing EPH-like receptors of the present invention is pDSR α which is described in Example 3. It is understood
20 that other vectors are also suitable for expression of EPH-like receptors in mammalian, yeast, insect or bacterial cells. In addition, in vivo expression of nucleic acids encoding EPH-like receptor PTKs is also encompassed. For example, tissue-specific expression of
25 EPH-like receptors in transgenic animals may be readily effected using vectors which are functional in selected tissues.

Host cells for the expression of EPH-like
30 receptor PTKs will preferably be established mammalian cell lines, such as Chinese Hamster Ovary (CHO) cells or NIH 3T3 cells, although other cell lines suitable for expression of mammalian genes are readily available and may also be used. Such host cells are transformed or
35 transfected with nucleic acid constructs suitable for expression of an EPH-like receptor. Transformed or

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transfected host cells may be used to produce suitable quantities of receptor for diagnostic or therapeutic uses and to effect targeted expression of EPH-like receptors in selected adult tissues, such as brain, kidney, and liver, or in embryonic or rapidly dividing tissues.

The present invention provides purified and isolated polypeptides having at least one of the biological properties of an EPH-like receptor (e.g. ligand binding, signal transduction). The isolated polypeptides will preferably have an amino acid sequence as shown in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16. Polypeptides of this invention may be full-length polypeptides having an extracellular domain, a transmembrane domain, and a cytoplasmic domain, or may be fragments thereof, e.g., those having only an extracellular domain or a portion thereof. It will be understood that the receptor polypeptides may also be analogs or naturally-occurring variants of the amino acid sequences shown in SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16. Such analogs are generated by amino acid substitutions, deletions and/or insertions using methods available in the art.

Polypeptides of the invention are preferably the product of expression of an exogenous DNA sequences, i.e., EPH-like receptors are preferably produced by recombinant means. Methods of producing EPH-like receptors comprising culturing host cells which have been transformed or transfected with vectors expressing an EPH-like receptor are also encompassed. EPH-like receptors, particularly fragments, may also be produced by chemical synthesis. The polypeptides so produced may be glycosylated or nonglycosylated depending upon the host cell employed, or may have a methionine residue at the amino terminal end. The polypeptides so produced

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are identified and recovered from cell cultures employing methods which are conventional in the art.

EPH-like receptors of the present invention are used for the production of antibodies to the
5 receptors. Antibodies to HEK receptors have been described in Example 4. Antibodies which recognize the polypeptides of the invention may be polyclonal or monoclonal and may be binding fragments or chimeric
10 ~~antibodies.~~ Such antibodies are useful in the detection of EPH-like receptors in diagnostic assays in the purification of receptor, and in the modulation of EPH-like receptor activation.

As described in co-pending and co-owned U.S. Serial No. 08/145,616, the only known ligand for an
15 EPH-like receptor is a protein which binds to and induces phosphorylation of the eck receptor. The ECK receptor ligand was previously identified as B61. (Holzman et al. Mol. Cell. Biol. 10, 5830-5838 (1990)).
20 The availability of ECK receptor was important for the identification of a ligand since B61, although known, had not been previously implicated as an ECK receptor ligand. Therefore, EPH-like receptors having ligand binding domains are useful for the identification and
25 purification of ligands. Polypeptides of the present invention may be used to identify and purify ligands for HEK5, HEK7, HEK8 and HEK11 receptors. Binding assays for the detection of potential ligands may be carried out in solution or by receptor immobilization on a solid
30 support using methods such as those described in co-pending and co-owned U.S. Serial No. 08/145,616. Such assays may employ an isolated ligand binding domain of a HEK receptor. Alternatively, a HEK ligand binding domain fused to an Ig domain may be used to detect the
35 presence of HEK ligand on cell surfaces.

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Soluble EPH-like receptors may be used to modulate (i.e., increase or decrease) the activation of the cell-associated receptors, typically by competing with the receptor for unbound ligand. Modulation of EPH-like receptor activation may, in turn alter the proliferation and/or differentiation of receptor-bearing cells. For example, based upon the observed tissue distribution of the receptors of this invention (see Table 5), soluble HEK7 receptor is likely to primarily affect proliferation and/or differentiation of brain cells, while soluble HEK5 receptor may affect primarily brain and pancreatic cells, although effects of HEK5 receptor on other tissues may not be excluded.

Antibodies to EPH-like receptors are useful reagents for the detection of receptors in different cell types using immunoassays conventional to the art. Antibodies are also useful therapeutic agents for modulating receptor activation. Antibodies may bind to the receptor so as to directly or indirectly block ligand binding and thereby act as an antagonist of receptor activation. Alternatively, antibodies may act as an agonist by binding to receptor so as to facilitate ligand binding and bring about receptor activation at lower ligand concentrations. In addition, antibodies of the present invention may themselves act as a ligands by inducing receptor activation. It is also contemplated that antibodies to EPH-like receptors are useful for selection of cell populations enriched for EPH-like receptor bearing cells. Such populations may be useful in cellular therapy regimens where it is necessary to treat patients which are depleted for certain cell types.

The isolated nucleic acids of the present inventions may be used in hybridization assays for the detection and quantitation of DNA and/or RNA coding for HEK5, HEK7, HEK8, HEK11 and related receptors. Such

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assays are important in determining the potential of various cell types to express these receptors and in determining actual expression levels of HEK receptors. In addition, the nucleic acids are useful for detecting abnormalities in HEK receptor genes, such as translocations, rearrangements, duplications, etc.

Therapeutic regimens involving EPH-like receptors will typically involve use of the soluble form of the receptor contained in a pharmaceutical composition. Such pharmaceutical compositions may contain pharmaceutically acceptable carrier, diluents, fillers, salts, buffers, stabilizers and/or other materials well known in the art. Further examples of such constituents are described in Remington's Pharmaceutical Sciences 18th ed., A.R. Gennaro, ed. (1990). Administration of soluble EPH-like receptor compositions may be by a variety of routes depending upon the condition being treated, although typically administration will occur by intravenous or subcutaneous methods. Pharmaceutical compositions containing antibodies to EPH-like receptors will preferably include mouse-human chimeric antibodies or CDR-grafted antibodies in order to minimize the potential for an immune response by the patient to antibodies raised in mice. Other components of anti-EPH antibody compositions will be similar to those described for soluble receptor.

The amount of soluble Eph-like receptors or anti-Eph antibody in a pharmaceutical composition will depend upon the nature and severity of the condition being treated. Said amount may be determined for a given patient by one skilled in the art. It is contemplated that the pharmaceutical compositions of the present invention will contain about 0.01 μ g to about

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100 mg of soluble receptor or anti-Eph antibody per kg body weight.

A method for modulating the activation of an EPH-like receptor PTK is also provided by the invention. In practicing this method, a therapeutically effective amount of a soluble EPH-like receptor or an anti-EPH antibody is administered. The term "therapeutically effective amount" is that amount which effects an increase or decrease in the activation of an EPH-like receptor and will range from about 0.01 μ g to about 100 mg of soluble receptor or anti-EPH antibody per kg body weight. In general, therapy will be appropriate for a patient having a condition treatable by soluble receptor or anti-EPH antibody and it is contemplated that such a condition will in part be related to the state of proliferation and/or differentiation of receptor-bearing cells. Based upon the tissue distribution of HEK receptors shown in Table 4, treatment with the pharmaceutical compositions of the invention may be particularly indicated for disorders involving brain, heart, muscle, lung, or pancreas. However, some HEK receptors are displayed on a wide variety of tissues, so it is understood that the effects of modulating receptor activation may not be limited to those tissues described herein.

The following examples are offered to more fully illustrate the invention, but are not to be construed as limiting the scope thereof. Recombinant DNA methods used in the following examples are generally as described in Sambrook et al. Molecular Cloning: A Laboratory Manual Cold Spring Harbor Laboratory Press, 2nd ed. (1989)

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EXAMPLE 1

Cloning and Sequencing of HEK Receptor cDNA

We have isolated clones for five members of the EPH sub-family of receptor PTKs from a human fetal brain cDNA library. Oligonucleotides were designed based on conserved amino acid sequences within the kinase domain. Primer I was based on the amino acid sequence Trp-Thr-Ala-Pro-Glu-Ala-Ile (SEQ ID NO: 1), which is well-conserved among PTKs of many families. Primer II was based on the sequence Val-Cys-Lys-Val-Ser-Asp-Phe-Gly (SEQ ID NO: 2), which is invariant among EPH sub-family members but, except for the sequence Asp-Phe-Gly, is rarely found in other PTKs. Fully degenerate oligonucleotides corresponding to reverse translations of these protein sequences were synthesized and utilized as primers in a polymerase chain reaction (PCR) with disrupted phage from a human fetal brain cDNA library as the template. The products of this PCR reaction were cloned into the plasmid vector pUC19 and the nucleotide sequence of the inserts was determined. Of the 35 PCR inserts sequenced, 27 were recognizable as portions of PTK genes. Their correspondence to previously published sequences is summarized in Table 1.

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TABLE 1

Receptor	PCR Products	Number of Clones
Elk	VCKVSDFGLSRYLQDDTSDPTTSSLGKIPVRWTAPEAI (SEQ ID NO: 3)	2
HEK4, HEK7	VCKVSDFGLSRVLEDDPEAAVTT RGGKIPIRWTAPEAI (SEQ ID NO: 4)	5*
HEK5	VCKVSDFGLSRFLEDDTSDPTTSSALGGKIPIRWTAPEAI (SEQ ID NO: 5)	8
HEK8	VCKVSDFGMSRVLEDDPEAAVTT RGGKIPIRWTAPEAI (SEQ ID NO: 6)	4
HEK11	VCKVSDFGLSRVIEDDPEAVVTTT GGGKIPVRWTAPEAI (SEQ ID NO: 7)	1
SRC	VCKVSDFGGLAR LIEDNEYTAHQ GAKFPIKWTAPEAI (SEQ ID NO: 8)	6*
PDGF- β	VCKVSDFGGLARDIMRDSNYISK GSTFLPLKWTAPEAI (SEQ ID NO: 9)	1

An asterisk indicates that different nucleic acid sequences encoded the amino acid sequence shown.

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Six PCR inserts predict amino acid sequences which are identical to a portion of SRC, although they comprise two distinct nucleotide sequences. One insert appears to code for the human platelet derived growth factor (PDGF)- β receptor. The remaining 18 PCR inserts consist of 6 distinct nucleotide sequences, all of which appear to be fragments of EPH sub-family members. One of the sequence predicts an amino acid sequence identical to the corresponding region of rat Elk (Lhotak et al., 1991)) and is likely to represent its human homolog. Two inserts predict amino acid sequences which match the translation of the PCR fragment tyro-4 (Lai and Lemke, 1991)) but are clearly distinct at the nucleotide level while two others correspond to tyro-1 and tyro-5. The sixth PCR insert has a previously unreported EPH-related sequence. Since five of the clones contained portions of potential EPH sub-family members for which full-length sequences had not been reported, each was radiolabeled and used as a probe to screen a human fetal brain cDNA library. Several clones corresponding to each of the five probes were isolated. For each of the five receptors, the nucleotide sequence of the clone containing the largest portion of the predicted coding region was determined.

25

A single cDNA clone containing the complete coding region was isolated only for HEK4. The portions of HEK5, HEK7, HEK10 and HEK11 coding for the amino terminus of these receptors were not found in any of the clones. In order to obtain the complete coding sequence, the Rapid Amplification of cDNA Ends (RACE) technique was employed. In some cases, more than one round of RACE was necessary to obtain the missing portion of the coding region. Using this strategy, complete coding sequences were obtained for all clones except HEK7 which lacked the complete leader sequence.

30
35

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The DNA sequences of HEK5, HEK7, HEK8 and HEK11 are shown in Figures 1-4, respectively, and in SEQ ID NO: 10 (HEK5), SEQ ID NO: 12 (HEK7), SEQ ID NO: 14 (HEK 8) and SEQ ID NO: 16 (HEK11). The amino acid sequences are shown in SEQ ID NO: 11 (HEK5), SEQ ID NO: 13 (HEK7), SEQ ID NO: 15 (HEK8) and SEQ ID NO: 17 (HEK 11).

EXAMPLE 2

10 Analysis of HEK Receptor Sequences

HEK5, HEK7, HEK8 and HEK11 represent novel human EPH sub-family members, although homologs for all except HEK11 have been isolated from other species. We refer to human EPH receptor sub-family members as HEKs (human EPH-like kinases) following the nomenclature of Wicks et al., 1992). We have chosen names and numbers for these receptors to correspond with previously discovered members of the family in chicken (Ceks) and in mouse (Mek) (Sajjadi et al. 1991; Sajjadi and Pasquale, 1993; Pasquale, 1991). Extending the convention of designating the species of origin by the first letter, we refer to the rat homologs of the HEK receptors as Reks (rat EPH-like kinases).

25 HEK4 is the human homolog of the chicken receptor Cek4 (91% amino acid identity in the catalytic domain) and the mouse receptor Mek4 (96% amino acid identity in the catalytic domain). The amino acid sequence of HEK5 is very closely related (96% amino acid identity in the catalytic domain) to the chicken receptor Cek5 (Pasquale et al. J. Neuroscience 12, 3956-3967 (1992); Pasquale, 1991). HEK7 is probably the human homolog of the recently reported Cek7 (Sajjadi and Pasquale, 1993). HEK8 is likewise very closely related to Sek (Gilardi-Hebenstreit et al., 1992)) and Cek8 (95% amino acid identity in the catalytic domain) (Sajjadi

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and Pasquale, 1993)). The human homologs for Cek6 and Cek9 have yet to be reported, while the human homolog of Cek10 has just recently been published. One of our human receptors has no close relatives in other species and apparently represents a novel member of the EPH sub-family. We have designated this receptor HEK11, assuming that human homologs for Cek 9 and 10 will be named HEK9 and HEK10, respectively. A summary of known EPH sub-family members is shown in Table 2.

10

TABLE 2

EPH receptor sub-family members

15	<u>Human</u>	<u>Non-human homologs</u>
	EPH	None identified
	ECK	None identified
	None identified#	Eek
	HEK4*	Cek4, Mek4
20	HEK5	Cek5, Nuk, ERK
	None identified#	Cek6, Elk
	HEK7	Cek7, Ehk1
	HEK8	Cek8, Sek
	None identified#	Cek9
25	HEK2	Cek10
	HEK11	None identified
	None identified	Ehk2

*published by Wicks et.al., 1992 as HEK

30 #Using the present nomenclature, the predicted human homolog of Eek is designated HEK3. For Cek6, the predicted human homolog is designated HEK6; For Cek9, the predicted human homolog is designated HEK9.

- 20 -

The predicted amino acid sequences of the four novel receptor clones and the previously known EPH sub-family members ECK (SEQ ID NO: 18), EPH (SEQ ID NO: 19), HEK2 (SEQ ID NO: 20) and HEK4 (SEQ ID NO: 21) were aligned as shown in Fig. 5. The four clones are closely related to each other and to the known EPH sub-family members. The extracellular domain sequences of all four novel receptors contain the Ig-loop, fibronectin-type III repeats, and cysteine-rich region characteristic of EPH sub-family members. The positions of the 20 cysteine residues are conserved among all sub-family members. Also completely conserved is the portion of the catalytic domain used as the basis for the EPH sub-family specific primer (Val-Cys-Lys-Val-Ser-Asp-Phe-Gly, SEQ ID NO: 2, amino acids 757-764 in Fig. 5). Table 3 summarizes the percentage of sequence identity between pairs of human EPH sub-family members. The lower portion of the table shows percent amino acid identity in the catalytic domain while the upper half shows percent amino acid identity in the extracellular region. The amino acid sequences of the EPH-like receptors are extremely well-conserved (60-89% amino acid identity) in the catalytic region but not as highly conserved in the extracellular region (38-65% amino acid identity), as would be expected for members of the same receptor sub-family.

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TABLE 3

Eph family amino acid sequence comparison

	extracellular domains							
	EPH	ECK	HEK4	HEK5	HEK7	HEK8	HEK2	HEK11
EPH	*	47	42	38	40	43	40	42
ECK	62	*	47	41	45	46	41	46
HEK4	62	76	*	53	65	61	51	59
HEK5	60	74	81	*	52	53	63	51
HEK7	61	76	89	83	*	62	48	61
HEK8	62	76	86	85	88	*	52	57
HEK2	61	74	81	89	82	83	*	48
HEK11	60	74	83	83	85	85	80	*

5 Catalytic domains

Numbers shown are percent identity

10 Pairwise comparisons of amino acid sequences can be used to construct phylogenetic trees depicting the evolutionary relatedness of a family of molecules. Figure 6 is such a tree, which summarizes the relationships among the EPH sub-family members. Only

15 one family member is shown from each group of cross-species homologs and the human representative was used whenever possible (refer to Table 2 for a summary of cross-species homologs). The branch lengths represent the degree of divergence between members. It has been

20 shown previously that the EPH sub-family lies on a branch evolutionarily closer to the cytoplasmic PTKs than to other receptor PTKs (Lindberg and Hunter, 1993). Interestingly, the further one moves up the tree, the more closely related the receptors become and expression

25 becomes more localized to the brain.

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EXAMPLE 3

Construction and Expression of HEK Receptor
Extracellular Domains

5 Soluble extracellular forms of HEK receptor
proteins were constructed by deletion of DNA sequences
encoding transmembrane and cytoplasmic domains of the
receptors and introduction of a translation stop codon
at the 3' end of the extracellular domain. A construct
10 of the HEK5 extracellular domain had a stop codon
introduced after lysine at position 524 as shown in
Figure 1; the HEK7 extracellular domain was constructed
with a stop codon after glutamine at position 547 as
shown in Figure 2; the HEK 8 extracellular domain was
15 constructed with a stop codon after threonine at
position 547 as shown in Figure 3.

HEK extracellular domain was amplified from a
human fetal brain cDNA library by PCR using primers 5'
and 3' to the extracellular domain coding region.

20 For HEK5, the primers

5' CTGCTCGCCGCGCGTGGAAGAAACG (SEQ ID NO: 22) and;
5' GCGTCTAGATTATCACTTCTCCTGGATGCTTGTCTGGTA (SEQ ID
NO: 23)

25 were used to amplify the extracellular domain and to
provide a restriction site for cloning into plasmid
pDSR α . In addition, the following primers were used to
provide a translational start site, the elk receptor
30 signal peptide for expression; and a restriction site
for cloning into pDSR α :

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5' GCGGTCGACGCCGCCGCCATGGCCCTGGATTGCCTGCTGCTGTTTCCTCCTG
(SEQ ID NO: 24) and;

5' CGTTTCTTCCACGGCGGCGAGCAGAGATGCCAGGAGGAACAGCAGCAGGCA
5 ATC (SEQ ID NO: 25)

The resulting construct resulted in fusion of
DNA encoding the elk signal sequence Met-Ala-Leu-Asp-
Cys-Leu-Leu-Leu-Phe-Leu-Leu-Ala-Ser (SEQ ID NO: 26) to
10 the first codon of the HEK5 receptor.

The resulting HEK5 extracellular domain was
cloned into pDSR α after digestion with SalI and XbaI and
transfected into CHO cells for expression.

HEK8 extracellular domain was amplified from a
15 human fetal brain cDNA library by PCR using primers 5'
and 3' to the extracellular domain coding region. For
HEK8, the primers

5' GAATTCGTCGACCCGGCGAACCATGGCTGGGAT and
20 5' GAATTCTCTAGATTATCATGTGGAGTTAGCCCCATCTC

were used to amplify the extracellular domain and to
provide restriction sites for cloning into plasmid
pDSR α .

25 The resulting HEK8 extracellular domain was
cloned into pDSR α after digestion with SalI and XbaI and
transferred CHO cells for expression.

HEK7 extracellular domain was amplified from a
human fetal brain cDNA library by PCR using primers 5'
30 and 3' to the extracellular domain coding region. For
HEK7, the primers

5'TTCGCCCTATTTTCGTGTCTCTTCGGGATTTGCGACGCTCTCCGGACCCTCCTG
GCCAGC and
35 5' GAATTCTCTAGATTATCACTGGCTTTGATCGCTGGAT

- 24 -

were used to amplify the extracellular domain. In addition, the following primers were used to provide a translational start site, the HEK8 receptor signal peptide sequence, and restriction site for cloning into plasmid pDSR α .

5' GAATTCGTCGACCCGGCGAACCATGGCTGGGATTTTCTATTTGCCCCTATTTTCGTGTCT
10 5' GAATTCTCTAGATTATCACTGGCTTTGATCGCTGGAT

The resulting construct resulted in fusion of DNA incoding HEK8 signal sequence Met-Ala-Gly-Ile-Phe-Tyr-Phe-Ala-Leu-Phe-Ser-Cys-Leu-Phe-Gly-Ile-Cys-Asp to the first codon of the HEK7 receptor.

The resulting HEK7 extracellular domain was cloned into pDSR α after digestion with SalI and XbaI and transfected into CHO cells for expression.

20

EXAMPLE 4

Antibodies to HEK Receptors

Antibodies to HEK receptor proteins were generated which recognize the extracellular domain by using bacterial fusion proteins as the antigen. Antibodies were also generated which recognize the cytoplasmic domain by using synthetic peptides as the antigen.

The methodology employed has been previously described (Harlow and Lane, In Antibodies: A Laboratory Manual, 1988). For the extracellular domain antibodies, cDNAs were inserted into the PATH vector (see Table 4 for the regions of each receptor encoded by this construct). These constructs were expressed in bacteria and the resultant TrpE-fusion proteins were purified by SDS-polyacrylamide gel electrophoresis. For the

- 25 -

cytoplasmic domain anti-peptide antibodies, peptides were synthesized (see Table 4 for the sequences) and covalently coupled to keyhole limpet hemocyanin. The fusion proteins and coupled peptides were used as antigens in rabbits and antisera were generated and characterized as described (Harlow and Lane, 1988). Anti-peptide antibodies were affinity purified by using a SulfoLink kit (Pierce, Rockford IL).

10

TABLE 4

HEK Receptor Antigens

15	<u>Receptor</u>	<u>Peptide Sequences</u>	<u>Amino Acids in Fusion Protein</u>
	HEK4	CLETQSKNGPVPV	22-159
	HEK5	CRAQMNQIQSVEV	31-168
	HEK7	CMKVQLVNGMVPL	335-545
20	HEK8	CMRTQMQQMHGRMVPV	27-188
	HEK11	CQMLHLHGTGIQV	187-503

EXAMPLE 5

25

HEK/TrkB Chimeric Receptors

1. Generation of pSJA1 encoding rat trkB cytoplasmic domain.

All of the chimeric receptors are composed of the extracellular domain and the transmembrane region of one of the HEK receptors and the intracellular portion of rat trkB. To simplify each individual construction, an intermediate or parental plasmid, called RtrkB/AflII (or pSJA1), was generated. First, without altering the coded peptide sequence, an AflII site (CTTAAG) was introduced into position 2021 (cytosine at position 2021

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(C2021) to guanine at position 2026 (G2026, CTC AAG) of the rat trkB cDNA (Middlemas, et al., Mol. Cell. Biol. 11, 143-153 (1991)) by PCR aided mutagenesis. Briefly, PCR primers were synthesized based on the rat trkB cDNA sequence. Primer I encompassed C2003 to G2034 of the cDNA. This primer contained two mutations, a cytosine to thymine(T) substitution at position 2023 (C2023T) and an insertion of an adenine(A) in between T2013 and G2014. These mutations created the AflIII site at position C2021 and an additional XhoI site flanking the AflIII site. Primer II was in the reverse direction encompassing T2141 to A2165 of the cDNA which bore an ApaI site. The PCR fragment produced with these primers and the rat trkB cDNA template was digested with XhoI and ApaI enzymes and sub cloned into the XhoI and ApaI sites of an expression vector, pCDNA3 (InVitroGen), to generate pSJA1-b. Following, pSJA1-b was linearized with ApaI and ligated with a BanII digested rat trkB cDNA fragment (G2151 to G4697) to reconstitute a larger fragment (C2021 to G4697) including the coding sequence of the whole intracellular domain of the rat trkB protein (L442 to G790) and 1571 residues (A3131 to G4697) of the 1627 nucleotide 3'-end non-coding region of the cDNA.

2. Generation of HEK8/rat trkB (pSJA5) chimera.

HEK8/rat trkB chimera was generated with a similar strategy as mentioned above. A SalI/BsaI cDNA fragment was first isolated from plasmid TK10/FL13. This fragment included the nucleotide sequence from the beginning to T1689 of the HEK8 cDNA (Figure 3). Then, a pair of oligonucleotides was synthesized based on the HEK8 cDNA sequence. The sequence of the first oligonucleotide was the same as G1690 to C1740 of the Hek8 cDNA, with an additional C residue added to its 3'-end. The second oligonucleotide was in the reverse

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orientation of the HEK8 cDNA. It contained C1694 to C1740 of the HEK8 cDNA sequence and an additional five residue motif, TTAAG, at its 5'-end. These two oligonucleotides were kinased and annealed with equal molar ratio, to create a double strand DNA fragment with the sequence of G1690 to C1740 of the HEK8 cDNA and with the BsaI and the AflII cohesive ends at its 5' and 3' ends, respectively. This fragment was ligated together with the SalI/BsaI cDNA fragment into XhoI/AflII linearized pSJA1 to generate the HEK8/RtrkB (pSJA5) chimerical construct.

3. Generation of HEK11/rat trkB (pSJA6) chimera.

To generate the HEK11/rat trkB chimera, a SalI/AccI fragment covering the sequence of nucleotide C1 to T1674 of the HEK11 cDNA (Figure 4) was first isolated from plasmid TK19T3. Then, a pair of oligonucleotides was synthesized based on the HEK11 cDNA sequence. The first oligonucleotide had the same sequence as from nucleotide A1666 to T1691 of the HEK11 cDNA, which contained the AccI site. The second oligonucleotide was in the reverse orientation of the HEK11 cDNA. It encompassed G1895 to T1919 of the HEK11 cDNA sequence. An additional ten residue motif, CCCGCTTAAG, was added to the 5'-end of this oligonucleotide to introduce an AflII site, which would be used to link the external domain and the transmembrane region of the HEK11 receptor to the intracellular domain of the rat trkB cDNA cloned in pSJA1 in the same reading frame. PCR was performed with these oligonucleotides as primers and the HEK11 cDNA as template. The PCR fragment was digested with AccI and AflII enzymes and ligated with the SalI/AccI cDNA fragment and the XhoI/AflII linearized pSJA1 to generate the HEK11/rat trkB (pSJA6) chimerical construct.

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EXAMPLE 6

Tissue Distribution of HEK Receptors

5 The distribution of mRNA expression for HEK4, HEK5, HEK7, HEK8 and HEK11 receptors in human and rat tissues was examined by Northern blot hybridization.

 Rat total RNA was prepared from tissues using the method of Chomczynski and Sacchi (Anal. Biochem 162,
10 156-159 (1987)). The RNA was separated by formaldehyde-agarose electrophoresis and transferred to Hybond-N membranes (Amersham, Arlington Heights, IL) using 20X SSC (Maniatis et al. 1982). The membrane was dried at
15 80°C in vacuo for 30 minutes, then crosslinked for 3 minutes on a UV transilluminator (Fotodyne, New Berlin, WI). The membrane was prehybridized for 2 hours at 42°C in 50% formamide, 5X SSPE, 5X Denhardt's, 0.2% SDS, and 100 µg/ml denatured herring sperm DNA (Maniatis et al. 1982). Northern blots of human tissue were purchased
20 from Clontech (Palo Alto, CA). Probes were prepared by labeling the fragment of cDNA which encoded the extracellular domain of the receptor with ³²P-dCTP using a hexanucleotide random priming kit (Boehringer Mannheim, Indianapolis, IN) to a specific activity of at
25 least 1x10⁹ cpm/ug. The probe was hybridized to the membrane at a concentration of 1-5 ng/ml at 42°C for 24 to 36 hours in a buffer similar to the prehybridization buffer except that 1X Denhardt's was used. After
30 hybridization, the membranes were washed 2 times for 5 minutes each in 2X SSC, 0.1% SDS at room temperature followed by two 15 minute washes in 0.5X SSC, 0.1% SDS at 55°C. Blots were exposed for 1-2 weeks using Kodak XAR film (Kodak, Rochester, NY) with a Dupont Lightning Plus intensifying screen. The results are shown in
35 Figures 7-11.

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Homologs for HEK4 have been previously identified from mouse, chicken, and rat. In the adult mouse, expression is detected primarily in the brain and testis (Sajjadi et al. 1991). A slightly different
5 pattern was found in adult chicken tissues, with the main sources of expression being the brain, liver, and kidney. Lower levels of expression were detectable in the lung and heart (Marcellé & Eichmann, Oncogene 7, 2479-2487 (1992)). A fragment of the *Rek4* gene (tyro-4)
10 has been isolated and used to look at tissue expression in the adult rat (Sajjadi et al. 1991). The brain was the only tissue that expressed *Rek4* mRNA. However, RNA from lung or testis were not examined. Previous studies on *HEK4* only looked at the expression of the mRNA in
15 cell lines, where it was found in one pre-B cell line and two T-cell lines (Wicks et al. 1992). The significance of this with regard to *in vivo* expression remains to be determined. In this study we have looked at the *HEK4* expression in human tissues, and also the
20 expression of *Rek4* in rat tissues. The *HEK4* mRNA corresponds to a single transcript with a size of about 7 kb (Fig 7A). *HEK4* mRNA was most abundantly expressed in placenta, with lower levels present in heart, brain, lung, and liver. On prolonged exposures, trace amounts
25 of mRNA were detectable in kidney and pancreas. Expression in the rat was more similar to that detected in the mouse and chicken. *Rek4* was expressed at the lowest levels of any of the family members characterized herein. A transcript of about 7 kb was detectable in
30 rat lung, with a lower amount detectable in brain (Fig. 7B). Also, a 4 kb transcript was expressed in rat testis. Because the transcripts were barely detectable using total RNA, some of the other rat tissues may contain amounts of *Rek4* below the level of detection.

35

- 30 -

The expression of HEK5 in adult tissues has been previously studied in chicken and rat. Studies in the chicken have identified the Cek5 protein in the brain and liver, with a smaller protein detected in the intestine. In the rat, the tyro-5 fragment detected mRNA expression only in the adult brain, though intestine was not examined (Lai and Lemke, 1991). Our results show that HEK5 mRNA was expressed at much higher levels than HEK4 and was found as transcripts of several sizes. The most abundant mRNAs were of approximately 4.0 and 4.4 kb, with lesser amounts of higher molecular weight transcripts of 9.5 kb and longer (Fig. 8A). The HEK5 mRNA was most abundantly expressed in placenta, but was also highly expressed in brain, pancreas, kidney, muscle, and lung. Longer exposures of the blots revealed the presence of transcripts in heart and liver as well. The rat homolog of HEK5 (Rek5) showed a somewhat similar pattern of expression. Rek5 was most abundant in intestine, followed by brain, kidney, lung, thymus, stomach, and ovary (Fig. 8B). Expression was not detectable in testis, muscle, heart, or liver. During our analysis of this family, we concluded that the rat Erk fragment (Chan & Watt, 1991) likely encodes a portion of the Rek5 receptor. Erk expression was examined in several rat tissues and found only in the lung. The reason for the discrepancy between that report and what we and others (Lai & Lemke, 1991) have found is unclear.

Homologs for HEK8 have been identified from chicken, mouse, and rat. In the adult chicken, a single Cek8 transcript was found to be expressed at high levels in the brain, with expression also detected in the kidney, lung, muscle, and thymus. The expression of the mouse homolog of HEK8, Sek, has been detected as a single transcript with abundant expression in the adult

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brain and lower expression in the heart, lung and kidney. A fragment of *Rek8* (tyro-1) was used to look at expression in rat tissues, with expression found only in the brain (Lai & Lemke, 1991). We found that *HEK8* mRNA
5 was expressed at levels comparable to that of *HEK5*. Multiple transcripts were also observed, the most abundant at 7 kb and 5 kb. The highest level of mRNA expression was seen in the brain, although substantial levels were detected in other tissues including heart,
10 lung, muscle, kidney, placenta, and pancreas. Expression in liver was much lower than in the other tissues. The only difference in expression patterns between human and mouse was expression in human muscle, also seen for *Cek8* in chicken. Among the rat tissues,
15 *Rek8* was most highly expressed in the brain, followed by the lung, heart, and testis (Fig. 10B). In contrast to *HEK8*, expression of *Rek8* appeared to be lower in muscle and kidney, two tissues where *HEK8* was readily detectable. In addition, *Rek8* was not expressed as a
20 5.0 kb transcript, as it was not visible even on prolonged exposures.

During the analysis of this family, we deduced that *HEK7* is the human homolog of *Cek7*. The only
25 expression seen in adult chicken was an 8.5 kb transcript found in the brain (Sajjadi & Pasquale, 1993). Of the five EPH sub-family members described here, *HEK7* was the most restricted in its expression pattern. Analysis of human mRNA revealed significant
30 expression only in the brain, with a much lower level detectable in the placenta (Fig. 9A). Prolonged exposures did not reveal expression in any other tissue examined. Two prominent transcripts were found in brain, the most highly expressed with a size of 6 kb and
35 the other with a length of 9 kb. In the placenta, however, only the 9 kb transcript was detected. *Rek7*

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mRNA was expressed in a pattern similar to *HEK7*. The highest level of expression was found in brain, with a much lower level in ovary (Fig. 9B). The transcripts were of similar size as for *HEK7*, with the 6 kb transcript detected only in brain.

HEK11 was expressed as several transcripts, with major mRNAs of length 7.5, 6.0 and 3.0 kb and minor transcripts of 4.4 and 2.4 kb (Fig. 11A). All five mRNAs were expressed at the highest levels in brain, followed by heart. Placenta, lung and kidney had significant amounts of four of the five transcripts, with lower expression seen in muscle. Pancreas had barely detectable amounts of *HEK11* mRNA, while liver had no detectable *HEK11* transcript. *Rek11* had a similar pattern of expression, with four transcripts (10, 7.5, 3.5 and 3.0 kb) detected in brain (Fig. 11B).

The relative level of mRNA expression for each of the five receptors in all tissues studied is summarized in Table 5.

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TABLE 5

Tissue Distribution of HEK Receptors

Human	HEK4	HEK5	HEK7	HEK8	HEK11
Brain	++	++	++	+++	++
Heart	+	+	bd	++	+
Kidney	+	+	bd	+	+
Liver	+	+	bd	+	bd
Lung	+	+	bd	++	+
Muscle	+	+	bd	++	+
Pancreas	+	++	bd	+	bd
Placenta	+++	+++	bd	++	+

5

Rat	HEK4	HEK5	HEK7	HEK8	HEK11
Brain	+	++	+++	+++	++
Heart	bd	bd	bd	+	bd
Intestine	bd	+++	bd	bd	bd
Kidney	bd	++	bd	bd	bd
Liver	bd	bd	bd	bd	bd
Lung	+	+	bd	++	bd
Muscle	bd	bd	bd	bd	bd
Ovary	bd	+	+	bd	bd
Stomach	bd	+	bd	bd	bd
Testis	+	bd	bd	+	bd
Thymus	bd	+	bd	bd	bd

bd= below detection

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The transcripts for *HEKs* 4,5,8, and 11 were rather widely distributed in human tissue while *HEK7* was specific for brain. Expression patterns between rat and human tissue were roughly comparable given that the rat blots were less sensitive due to the use of total RNA rather than polyA⁺. As was found for the *Cek* mRNAs by Sajjadi and Pasquale (Sajjadi & Pasquale, 1993), often there were several different size transcripts detected for a single receptor. The size distribution of the transcripts appears to be both tissue and species specific. Previous work has shown that the smaller transcript of *Mek4* encodes a potentially secreted receptor (Sajjadi et al. 1991).

The following sections describe Materials and Methods used to carry out experiments described in Example 1.

Isolation, cloning and sequencing of HEK receptor cDNAs

Fragments containing a portion of the catalytic domain of EPH sub-family receptors were generated using a polymerase chain reaction (PCR) with disrupted phage from a human fetal brain cDNA library as a template. A 10 μ l aliquot of the cDNA library (Stratagene, La Jolla, CA) was treated at 70°C for 5 minutes to disrupt the phage particles, then cooled on wet ice. The disrupted phage were added to 10 μ l of 10X *Taq* polymerase buffer, 8 μ l of 2mM each dNTP, 100 picomoles of each primer, and 1.5 μ l of *Taq* polymerase (Promega, Madison, WI) in a total volume of 100 μ l. The reaction was run for 35 cycles, each consisting of 1 minute at 96°C, 1 minute at 50°C, and 2 minutes at 72°C. A 5 minute, 72°C incubation was added at the end to ensure complete extension. The primers used were degenerate mixtures of oligonucleotides based on amino

- 35 -

acid sequences which are highly conserved among EPH sub-family members.

5'AGGGAATTCCAYCGNGAYYTNGCNGC' (SEQ ID NO: 27);

5 5'AGGGGATCCRWARSWCCANACRTC' (SEQ ID NO: 28).

The products of the PCR reaction were digested with EcoRI and BamHI and cloned into M13mp19 (Messing, Methods Enzymol. (1983)) for sequence analysis. The
10 five clones which were identified as fragments of EPH receptor sub-family members were labeled with ³²P-dCTP by random priming and each was used to screen Genescreen nitrocellulose filters (NEN, Boston, MA) containing
15 plaques from the human fetal brain cDNA library. Phage stocks prepared from positively screening plaques were plated and rescreened with the same probe in order to obtain single clones. cDNA inserts were transferred into pBluescript using the *in vivo* excision protocol
20 supplied with the cDNA library (Stratagene, La Jolla, CA). Nucleotide sequences were determined using Taq DyeDeoxy Terminator Cycle Sequencing kits and an Applied Biosystems 373A automated DNA sequencer (Applied Biosystems, Foster City, CA).

25 5' Race

The 5' ends of the cDNAs were isolated using a 5' RACE kit (GIBCO/BRL, Gaithersburg, MD) following the manufacturer's instructions. Excess primers were removed after first strand cDNA synthesis using
30 ultrafree-MC cellulose filters (30,000 molecular weight cutoff, Millipore, Bedford, MA). Amplified PCR products were digested with the appropriate restriction enzymes, separated by agarose gel electrophoresis, and purified using a Geneclean kit (Bio101, La Jolla, CA). The
35 purified PCR product was ligated into the plasmid vector pUC19 (Yanisch-Perron et al. Gene 33, 103-119 (1985))

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which had been digested with appropriate restriction enzymes and the ligation mixture was introduced into host bacteria by electroporation. Plasmid DNA was prepared from the resulting colonies. Those clones with
5 the largest inserts were selected for DNA sequencing.

While the present invention has been described
10 in terms of preferred embodiments, it is understood that variations and modifications will occur to those skilled in the art. Therefore, it is intended that the appended claims cover all such equivalent variations which come
15 within the scope of the invention as claimed.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: Amgen Inc.
- (ii) TITLE OF INVENTION: EPH-Like Receptor Protein Tyrosine Kinases
- (iii) NUMBER OF SEQUENCES: 28
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Amgen Patent Operations/RBW
 - (B) STREET: 1840 Dehavilland Drive
 - (C) CITY: Thousand Oaks
 - (D) STATE: California
 - (E) COUNTRY: USA
 - (F) ZIP: 91320
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Floppy disk
 - (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: PatentIn Release #1.0, Version #1.25
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER:
 - (B) FILING DATE:
 - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Winter, Robert B.
 - (C) REFERENCE/DOCKET NUMBER: A-287

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 7 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Trp	Thr	Ala	Pro	Glu	Ala	Ile
1				5		

- 38 -

(2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Val Cys Lys Val Ser Asp Phe Gly
1 5

(2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Tyr Leu Gln Asp Asp
1 5 10 15
Thr Ser Asp Pro Thr Tyr Thr Ser Ser Leu Gly Gly Lys Ile Pro Val
20 25 30
Arg Trp Thr Ala Pro Glu Ala Ile
35 40

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val Leu Glu Asp Asp
1 5 10 15

- 39 -

Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp
 20 25 30

Thr Ala Pro Glu Ala Ile
 35

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 40 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Phe Leu Glu Asp Asp
 1 5 10 15

Thr Ser Asp Pro Thr Tyr Thr Ser Ala Leu Gly Gly Lys Ile Pro Ile
 20 25 30

Arg Trp Thr Ala Pro Glu Ala Ile
 35 40

(2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 38 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Val Cys Lys Val Ser Asp Phe Gly Met Ser Arg Val Leu Glu Asp Asp
 1 5 10 15

Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp
 20 25 30

Thr Ala Pro Glu Ala Ile
 35

- 40 -

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val Ile Glu Asp Asp
1 5 10 15
Pro Glu Ala Val Tyr Thr Thr Thr Gly Gly Lys Ile Pro Val Arg Trp
20 25 30
Thr Ala Pro Glu Ala Ile
35

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Val Cys Lys Val Ser Asp Phe Gly Leu Ala Arg Leu Ile Glu Asp Asn
1 5 10 15
Glu Tyr Thr Ala Arg Gln Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala
20 25 30
Pro Glu Ala Ile
35

(2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Val Cys Lys Val Ser Asp Phe Gly Leu Ala Arg Asp Ile Met Arg Asp
 1 5 10 15
 Ser Asn Tyr Ile Ser Lys Gly Ser Thr Phe Leu Pro Leu Lys Trp Thr
 20 25 30
 Ala Pro Glu Ala Ile
 35

(2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2962 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 1..2913

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CTG CTC GCC GCC GTG GAA GAA ACG CTA ATG GAC TCC ACT ACA GCG ACT	48
Leu Leu Ala Ala Val Glu Glu Thr Leu Met Asp Ser Thr Thr Ala Thr	
1 5 10 15	
GCT GAG CTG GGC TGG ATG GTG CAT CCT CCA TCA GGG TGG GAA GAG GTG	96
Ala Glu Leu Gly Trp Met Val His Pro Pro Ser Gly Trp Glu Glu Val	
20 25 30	
AGT GGC TAC GAT GAG AAC ATG AAC ACG ATC CGC ACG TAC CAG GTG TGC	144
Ser Gly Tyr Asp Glu Asn Met Asn Thr Ile Arg Thr Tyr Gln Val Cys	
35 40 45	
AAC GTG TTT GAG TCA AGC CAG AAC AAC TGG CTA CGG ACC AAG TTT ATC	192
Asn Val Phe Glu Ser Ser Gln Asn Asn Trp Leu Arg Thr Lys Phe Ile	
50 55 60	
CGG CGC CGT GGG GCC CAC CGC ATC CAC GTG GAG ATG AAG TTT TCG GTG	240
Arg Arg Arg Gly Ala His Arg Ile His Val Glu Met Lys Phe Ser Val	
65 70 75 80	
CGT GAC TGC AGC AGC ATC CCC AGC GTG CCT GGC TCC TGC AAG GAG ACC	288
Arg Asp Cys Ser Ser Ile Pro Ser Val Pro Gly Ser Cys Lys Glu Thr	
85 90 95	
TTC AAC CTC TAT TAC TAT GAG GCT GAC TTT GAC TCG GCC ACC AAG ACC	336
Phe Asn Leu Tyr Tyr Tyr Glu Ala Asp Phe Asp Ser Ala Thr Lys Thr	
100 105 110	

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TTC CCC AAC TGG ATG GAG AAT CCA TGG GTG AAG GTG GAT ACC ATT GCA Phe Pro Asn Trp Met Glu Asn Pro Trp Val Lys Val Asp Thr Ile Ala 115 120 125	384
GCC GAC GAG AGC TTC TCC CAG GTG GAC CTG GGT GGC CGC GTC ATG AAA Ala Asp Glu Ser Phe Ser Gln Val Asp Leu Gly Gly Arg Val Met Lys 130 135 140	432
ATC AAC ACC GAG GTG CGG AGC TTC GGA CCT GTG TCC CGC AGC GGC TTC Ile Asn Thr Glu Val Arg Ser Phe Gly Pro Val Ser Arg Ser Gly Phe 145 150 155 160	480
TAC CTG GCC TTC CAG GAC TAT GGC GGC TGC ATG TCC CTC ATC GCC GTG Tyr Leu Ala Phe Gln Asp Tyr Gly Gly Cys Met Ser Leu Ile Ala Val 165 170 175	528
CGT GTC TTC TAC CGC AAG TGC CCC CGC ATC ATC CAG AAT GGC GCC ATC Arg Val Phe Tyr Arg Lys Cys Pro Arg Ile Ile Gln Asn Gly Ala Ile 180 185 190	576
TTC CAG GAA ACC CTG TCG GGG GCT GAG AGC ACA TCG CTG GTG GCT GCC Phe Gln Glu Thr Leu Ser Gly Ala Glu Ser Thr Ser Leu Val Ala Ala 195 200 205	624
CGG GGC AGC TGC ATC GCC AAT GCG GAA GAG GTG GAT GTA CCC ATC AAG Arg Gly Ser Cys Ile Ala Asn Ala Glu Glu Val Asp Val Pro Ile Lys 210 215 220	672
CTC TAC TGT AAC GGG GAC GGC GAG TGG CTG GTG CCC ATC GGG CGC TGC Leu Tyr Cys Asn Gly Asp Gly Glu Trp Leu Val Pro Ile Gly Arg Cys 225 230 235 240	720
ATG TGC AAA GCA GGC TTC GAG GCC GTT GAG AAT GGC ACC GTC TGC CGA Met Cys Lys Ala Gly Phe Glu Ala Val Glu Asn Gly Thr Val Cys Arg 245 250 255	768
GGT TGT CCA TCT GGG ACT TTC AAG GCC AAC CAA GGG GAT GAG GCC TGT Gly Cys Pro Ser Gly Thr Phe Lys Ala Asn Gln Gly Asp Glu Ala Cys 260 265 270	816
ACC CAC TGT CCC ATC AAC AGC CGG ACC ACT TCT GAA GGG GCC ACC AAC Thr His Cys Pro Ile Asn Ser Arg Thr Thr Ser Glu Gly Ala Thr Asn 275 280 285	864
TGT GTC TGC CGC AAT GGC TAC TAC AGA GCA GAC CTG GAC CCC CTG GAC Cys Val Cys Arg Asn Gly Tyr Tyr Arg Ala Asp Leu Asp Pro Leu Asp 290 295 300	912
ATG CCC TGC ACA ACC ATC CCC TCC GCG CCC CAG GCT GTG ATT TCC AGT Met Pro Cys Thr Thr Ile Pro Ser Ala Pro Gln Ala Val Ile Ser Ser 305 310 315 320	960
GTC AAT GAG ACC TCC CTC ATG CTG GAG TGG ACC CCT CCC CGC GAC TCC Val Asn Glu Thr Ser Leu Met Leu Glu Trp Thr Pro Pro Arg Asp Ser 325 330 335	1008

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GGA	GGC	CGA	GAG	GAC	CTC	GTC	TAC	AAC	ATC	ATC	TGC	AAG	AGC	TGT	GGC	1056
Gly	Gly	Arg	Glu	Asp	Leu	Val	Tyr	Asn	Ile	Ile	Cys	Lys	Ser	Cys	Gly	
			340					345					350			
TCG	GGC	CGG	GGT	GCC	TGC	ACC	CGC	TGC	GGG	GAC	AAT	GTA	CAG	TAC	GCA	1104
Ser	Gly	Arg	Gly	Ala	Cys	Thr	Arg	Cys	Gly	Asp	Asn	Val	Gln	Tyr	Ala	
		355					360					365				
CCA	CGC	CAG	CTA	GGC	CTG	ACC	GAG	CCA	CGC	ATT	TAC	ATC	AGT	GAC	CTG	1152
Pro	Arg	Gln	Leu	Gly	Leu	Thr	Glu	Pro	Arg	Ile	Tyr	Ile	Ser	Asp	Leu	
		370				375					380					
CTG	GCC	CAC	ACC	CAG	TAC	ACC	TTC	GAG	ATC	CAG	GCT	GTG	AAC	GGC	GTT	1200
Leu	Ala	His	Thr	Gln	Tyr	Thr	Phe	Glu	Ile	Gln	Ala	Val	Asn	Gly	Val	
385					390					395				400		
ACT	GAC	CAG	AGC	CCC	TTC	TCG	CCT	CAG	TTC	GCC	TCT	GTG	AAC	ATC	ACC	1248
Thr	Asp	Gln	Ser	Pro	Phe	Ser	Pro	Gln	Phe	Ala	Ser	Val	Asn	Ile	Thr	
				405					410					415		
ACC	AAC	CAG	GCA	GCT	CCA	TCG	GCA	GTG	TCC	ATC	ATG	CAT	CAG	GTG	AGC	1296
Thr	Asn	Gln	Ala	Ala	Pro	Ser	Ala	Val	Ser	Ile	Met	His	Gln	Val	Ser	
			420					425					430			
CGC	ACC	GTG	GAC	AGC	ATT	ACC	CTG	TCG	TGG	TCC	CAG	CCG	GAC	CAG	CCC	1344
Arg	Thr	Val	Asp	Ser	Ile	Thr	Leu	Ser	Trp	Ser	Gln	Pro	Asp	Gln	Pro	
		435					440					445				
AAT	GGC	GTG	ATC	CTG	GAC	TAT	GAG	CTG	CAG	TAC	TAT	GAG	AAG	GAG	CTC	1392
Asn	Gly	Val	Ile	Leu	Asp	Tyr	Glu	Leu	Gln	Tyr	Tyr	Glu	Lys	Glu	Leu	
	450					455					460					
AGT	GAG	TAC	AAC	GCC	ACA	GCC	ATA	AAA	AGC	CCC	ACC	AAC	ACG	GTC	ACG	1440
Ser	Glu	Tyr	Asn	Ala	Thr	Ala	Ile	Lys	Ser	Pro	Thr	Asn	Thr	Val	Thr	
465					470					475				480		
GGC	CTC	AAA	GCC	GGC	GCC	ATC	TAT	GTC	TTC	CAG	GTG	CGG	GCA	CGC	ACT	1488
Gly	Leu	Lys	Ala	Gly	Ala	Ile	Tyr	Val	Phe	Gln	Val	Arg	Ala	Arg	Thr	
				485				490						495		
GTG	GCA	GGC	TAC	GGG	CGC	TAC	AGC	GGC	AAG	ATG	TAC	TTC	CAG	ACC	ATG	1536
Val	Ala	Gly	Tyr	Gly	Arg	Tyr	Ser	Gly	Lys	Met	Tyr	Phe	Gln	Thr	Met	
			500					505					510			
ACA	GAA	GCC	GAG	TAC	CAG	ACA	AGC	ATC	CAG	GAG	AAG	TTG	CCA	CTC	ATC	1584
Thr	Glu	Ala	Glu	Tyr	Gln	Thr	Ser	Ile	Gln	Glu	Lys	Leu	Pro	Leu	Ile	
		515					520					525				
ATC	GGC	TCC	TCG	GCC	GCT	GGC	CTG	GTC	TTC	CTC	ATT	GCT	GTG	GTT	GTC	1632
Ile	Gly	Ser	Ser	Ala	Ala	Gly	Leu	Val	Phe	Leu	Ile	Ala	Val	Val	Val	
	530					535					540					
ATC	GCC	ATC	GTG	TGT	AAC	AGA	CGG	GGG	TTT	GAG	CGT	GCT	GAC	TCG	GAG	1680
Ile	Ala	Ile	Val	Cys	Asn	Arg	Arg	Gly	Phe	Glu	Arg	Ala	Asp	Ser	Glu	
545					550					555					560	

TAC ACG GAC AAG CTG CAA CAC TAC ACC AGT GGC CAC ATA ACC CCA GGC Tyr Thr Asp Lys Leu Gln His Tyr Thr Ser Gly His Ile Thr Pro Gly 565 570 575	1728
ATG AAG ATC TAC ATC GAT CCT TTC ACC TAC GAG GAC CCC AAC GAG GCA Met Lys Ile Tyr Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn Glu Ala 580 585 590	1776
GTG CGG GAG TTT GCC AAG GAA ATT GAC ATC TCC TGT GTC AAA ATT GAG Val Arg Glu Phe Ala Lys Glu Ile Asp Ile Ser Cys Val Lys Ile Glu 595 600 605	1824
CAG GTG ATC GGA GCA GGG GAG TTT GGC GAG GTC TGC AGT GGC CAC CTG Gln Val Ile Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly His Leu 610 615 620	1872
AAG CTG CCA GGC AAG AGA GAG ATC TTT GTG GCC ATC AAG ACG CTC AAG Lys Leu Pro Gly Lys Arg Glu Ile Phe Val Ala Ile Lys Thr Leu Lys 625 630 635 640	1920
TCG GGC TAC ACG GAG AAG CAG CGC CGG GAC TTC CTG AGC GAA GCC TCC Ser Gly Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser 645 650 655	1968
ATC ATG GGC CAG TTC GAC CAT CCC AAC GTC ATC CAC CTG GAG GGT GTC Ile Met Gly Gln Phe Asp His Pro Asn Val Ile His Leu Glu Gly Val 660 665 670	2016
GTG ACC AAG AGC ACA CCT GTG ATG ATC ATC ACC GAG TTC ATG GAG AAT Val Thr Lys Ser Thr Pro Val Met Ile Ile Thr Glu Phe Met Glu Asn 675 680 685	2064
GGC TCC CTG GAC TCC TTT CTC CGG CAA AAC GAT GGG CAG TTC ACA GTC Gly Ser Leu Asp Ser Phe Leu Arg Gln Asn Asp Gly Gln Phe Thr Val 690 695 700	2112
ATC CAG CTG GTG GGC ATG CTT CGG GGC ATC GCA GCT GGC ATG AAG TAC Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ala Gly Met Lys Tyr 705 710 715 720	2160
CTG GCA GAC ATG AAC TAT GTT CAC CGT GAC CTG GCT GCC CGC AAC ATC Leu Ala Asp Met Asn Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile 725 730 735	2208
CTC GTC AAC AGC AAC CTG GTC TGC AAG GTG TCG GAC TTT GGG CTC TCA Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser 740 745 750	2256
CGC TTT CTA GAG GAC GAT ACC TCA GAC CCC ACC TAC ACC AGT GCC CTG Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro Thr Tyr Thr Ser Ala Leu 755 760 765	2304
GGC GGA AAG TTC CCC ATC CGC TGG ACA GCC CCG GAA GCC ATC CAG TAC Gly Gly Lys Phe Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr 770 775 780	2352

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CGG AAG TTC ACC TCG GCC AGT GAT GTG TGG AGC TAC GGC ATT GTC ATG Arg Lys Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met 785 790 795 800	2400
TGG GAG GTG ATG TCC TAT GGG GAG CGG CCC TAC TGG GAC ATG ACC AAC Trp Glu Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Thr Asn 805 810 815	2448
CAG GAT GTA ATC AAT GCC ATT GAG CAG GAC TAT CGG CTG CCA CCG CCC Gln Asp Val Ile Asn Ala Ile Glu Gln Asp Tyr Arg Leu Pro Pro Pro 820 825 830	2496
ATG GAC TGC CCG AGC GCC CTG CAC CAA CTC ATG CTG GAC TGT TGG CAG Met Asp Cys Pro Ser Ala Leu His Gln Leu Met Leu Asp Cys Trp Gln 835 840 845	2544
AAG GAC CGC AAC CAC CGG CCC AAG TTC GGC CAA ATT GTC AAC ACG CTA Lys Asp Arg Asn His Arg Pro Lys Phe Gly Gln Ile Val Asn Thr Leu 850 855 860	2592
GAC AAG ATG ATC CGC AAT CCC AAC AGC CTC AAA GCC ATG GCG CCC CTC Asp Lys Met Ile Arg Asn Pro Asn Ser Leu Lys Ala Met Ala Pro Leu 865 870 875 880	2640
TCC TCT GGC ATC AAC CTG CCG CTG CTG GAC CGC ACG ATC CCC GAC TAC Ser Ser Gly Ile Asn Leu Pro Leu Leu Asp Arg Thr Ile Pro Asp Tyr 885 890 895	2688
ACC AGC TTT AAC ACG GTG GAC GAG TGG CTG GAG GCC ATC AAG ATG GGG Thr Ser Phe Asn Thr Val Asp Glu Trp Leu Glu Ala Ile Lys Met Gly 900 905 910	2736
CAG TAC AAG GAG AGC TTC GCC AAT GCC GGC TTC ACC TCC TTT GAC GTC Gln Tyr Lys Glu Ser Phe Ala Asn Ala Gly Phe Thr Ser Phe Asp Val 915 920 925	2784
GTG TCT CAG ATG ATG ATG GAG GAC ATT CTC CGG GTT GGG GTC ACT TTG Val Ser Gln Met Met Met Glu Asp Ile Leu Arg Val Gly Val Thr Leu 930 935 940	2832
GCT GGC CAC CAG AAA AAA ATC CTG AAC AGT ATC CAG GTG ATG CGG GCG Ala Gly His Gln Lys Lys Ile Leu Asn Ser Ile Gln Val Met Arg Ala 945 950 955 960	2880
CAG ATG AAC CAG ATT CAG TCT GTG GAG GTT TGACATTCAC CTGCCTCGGC Gln Met Asn Gln Ile Gln Ser Val Glu Val 965 970	2930
TCACCTCTTC CTCCAAGCCC CGCCCCCTCT GC	2962

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 970 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

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Leu Leu Ala Ala Val Glu Glu Thr Leu Met Asp Ser Thr Thr Ala Thr
 1           5           10           15
Ala Glu Leu Gly Trp Met Val His Pro Pro Ser Gly Trp Glu Glu Val
      20           25           30
Ser Gly Tyr Asp Glu Asn Met Asn Thr Ile Arg Thr Tyr Gln Val Cys
      35           40           45
Asn Val Phe Glu Ser Ser Gln Asn Asn Trp Leu Arg Thr Lys Phe Ile
      50           55           60
Arg Arg Arg Gly Ala His Arg Ile His Val Glu Met Lys Phe Ser Val
      65           70           75           80
Arg Asp Cys Ser Ser Ile Pro Ser Val Pro Gly Ser Cys Lys Glu Thr
      85           90           95
Phe Asn Leu Tyr Tyr Tyr Glu Ala Asp Phe Asp Ser Ala Thr Lys Thr
      100          105          110
Phe Pro Asn Trp Met Glu Asn Pro Trp Val Lys Val Asp Thr Ile Ala
      115          120          125
Ala Asp Glu Ser Phe Ser Gln Val Asp Leu Gly Gly Arg Val Met Lys
      130          135          140
Ile Asn Thr Glu Val Arg Ser Phe Gly Pro Val Ser Arg Ser Gly Phe
      145          150          155          160
Tyr Leu Ala Phe Gln Asp Tyr Gly Gly Cys Met Ser Leu Ile Ala Val
      165          170          175
Arg Val Phe Tyr Arg Lys Cys Pro Arg Ile Ile Gln Asn Gly Ala Ile
      180          185          190
Phe Gln Glu Thr Leu Ser Gly Ala Glu Ser Thr Ser Leu Val Ala Ala
      195          200          205
Arg Gly Ser Cys Ile Ala Asn Ala Glu Glu Val Asp Val Pro Ile Lys
      210          215          220
Leu Tyr Cys Asn Gly Asp Gly Glu Trp Leu Val Pro Ile Gly Arg Cys
      225          230          235          240
Met Cys Lys Ala Gly Phe Glu Ala Val Glu Asn Gly Thr Val Cys Arg
      245          250          255
Gly Cys Pro Ser Gly Thr Phe Lys Ala Asn Gln Gly Asp Glu Ala Cys
      260          265          270
Thr His Cys Pro Ile Asn Ser Arg Thr Thr Ser Glu Gly Ala Thr Asn
      275          280          285

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Cys Val Cys Arg Asn Gly Tyr Tyr Arg Ala Asp Leu Asp Pro Leu Asp
 290 295 300

Met Pro Cys Thr Thr Ile Pro Ser Ala Pro Gln Ala Val Ile Ser Ser
 305 310 315 320

Val Asn Glu Thr Ser Leu Met Leu Glu Trp Thr Pro Pro Arg Asp Ser
 325 330 335

Gly Gly Arg Glu Asp Leu Val Tyr Asn Ile Ile Cys Lys Ser Cys Gly
 340 345 350

Ser Gly Arg Gly Ala Cys Thr Arg Cys Gly Asp Asn Val Gln Tyr Ala
 355 360 365

Pro Arg Gln Leu Gly Leu Thr Glu Pro Arg Ile Tyr Ile Ser Asp Leu
 370 375 380

Leu Ala His Thr Gln Tyr Thr Phe Glu Ile Gln Ala Val Asn Gly Val
 385 390 395 400

Thr Asp Gln Ser Pro Phe Ser Pro Gln Phe Ala Ser Val Asn Ile Thr
 405 410 415

Thr Asn Gln Ala Ala Pro Ser Ala Val Ser Ile Met His Gln Val Ser
 420 425 430

Arg Thr Val Asp Ser Ile Thr Leu Ser Trp Ser Gln Pro Asp Gln Pro
 435 440 445

Asn Gly Val Ile Leu Asp Tyr Glu Leu Gln Tyr Tyr Glu Lys Glu Leu
 450 455 460

Ser Glu Tyr Asn Ala Thr Ala Ile Lys Ser Pro Thr Asn Thr Val Thr
 465 470 475 480

Gly Leu Lys Ala Gly Ala Ile Tyr Val Phe Gln Val Arg Ala Arg Thr
 485 490 495

Val Ala Gly Tyr Gly Arg Tyr Ser Gly Lys Met Tyr Phe Gln Thr Met
 500 505 510

Thr Glu Ala Glu Tyr Gln Thr Ser Ile Gln Glu Lys Leu Pro Leu Ile
 515 520 525

Ile Gly Ser Ser Ala Ala Gly Leu Val Phe Leu Ile Ala Val Val Val
 530 535 540

Ile Ala Ile Val Cys Asn Arg Arg Gly Phe Glu Arg Ala Asp Ser Glu
 545 550 555 560

Tyr Thr Asp Lys Leu Gln His Tyr Thr Ser Gly His Ile Thr Pro Gly
 565 570 575

Met Lys Ile Tyr Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn Glu Ala
 580 585 590

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Val Arg Glu Phe Ala Lys Glu Ile Asp Ile Ser Cys Val Lys Ile Glu
 595 600 605
 Gln Val Ile Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly His Leu
 610 615 620
 Lys Leu Pro Gly Lys Arg Glu Ile Phe Val Ala Ile Lys Thr Leu Lys
 625 630 635 640
 Ser Gly Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser
 645 650 655
 Ile Met Gly Gln Phe Asp His Pro Asn Val Ile His Leu Glu Gly Val
 660 665 670
 Val Thr Lys Ser Thr Pro Val Met Ile Ile Thr Glu Phe Met Glu Asn
 675 680 685
 Gly Ser Leu Asp Ser Phe Leu Arg Gln Asn Asp Gly Gln Phe Thr Val
 690 695 700
 Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ala Gly Met Lys Tyr
 705 710 715 720
 Leu Ala Asp Met Asn Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile
 725 730 735
 Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser
 740 745 750
 Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro Thr Tyr Thr Ser Ala Leu
 755 760 765
 Gly Gly Lys Phe Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr
 770 775 780
 Arg Lys Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met
 785 790 795 800
 Trp Glu Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Thr Asn
 805 810 815
 Gln Asp Val Ile Asn Ala Ile Glu Gln Asp Tyr Arg Leu Pro Pro Pro
 820 825 830
 Met Asp Cys Pro Ser Ala Leu His Gln Leu Met Leu Asp Cys Trp Gln
 835 840 845
 Lys Asp Arg Asn His Arg Pro Lys Phe Gly Gln Ile Val Asn Thr Leu
 850 855 860
 Asp Lys Met Ile Arg Asn Pro Asn Ser Leu Lys Ala Met Ala Pro Leu
 865 870 875 880
 Ser Ser Gly Ile Asn Leu Pro Leu Leu Asp Arg Thr Ile Pro Asp Tyr
 885 890 895

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Thr Ser Phe Asn Thr Val Asp Glu Trp Leu Glu Ala Ile Lys Met Gly
 900 905 910

Gln Tyr Lys Glu Ser Phe Ala Asn Ala Gly Phe Thr Ser Phe Asp Val
 915 920 925

Val Ser Gln Met Met Met Glu Asp Ile Leu Arg Val Gly Val Thr Leu
 930 935 940

Ala Gly His Gln Lys Lys Ile Leu Asn Ser Ile Gln Val Met Arg Ala
 945 950 955 960

Gln Met Asn Gln Ile Gln Ser Val Glu Val
 965 970

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3162 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..2976

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CCA GCG TCC CTG GCC GGC TGC TAC TCT GCA CCT CGA CGG GCT CCC CTC	48
Pro Ala Ser Leu Ala Gly Cys Tyr Ser Ala Pro Arg Arg Ala Pro Leu	
1 5 10 15	
TGG ACG TGC CTT CTC CTG TGC GCC GCA CTC CGG ACC CTC CTG GCC AGC	96
Trp Thr Cys Leu Leu Leu Cys Ala Ala Leu Arg Thr Leu Leu Ala Ser	
20 25 30	
CCC AGC AAC GAA GTG AAT TTA TTG GAT TCA CGC ACT GTC ATG GGG GAC	144
Pro Ser Asn Glu Val Asn Leu Leu Asp Ser Arg Thr Val Met Gly Asp	
35 40 45	
CTG GGA TGG ATT GCT TTT CCA AAA AAT GGG TGG GAA GAG ATT GGT GAA	192
Leu Gly Trp Ile Ala Phe Pro Lys Asn Gly Trp Glu Glu Ile Gly Glu	
50 55 60	
GTG GAT GAA AAT TAT GCC CCT ATC CAC ACA TAC CAA GTA TGC AAA GTG	240
Val Asp Glu Asn Tyr Ala Pro Ile His Thr Tyr Gln Val Cys Lys Val	
65 70 75 80	
ATG GAA CAG AAT CAG AAT AAC TGG CTT TTG ACC AGT TGG ATC TCC AAT	288
Met Glu Gln Asn Gln Asn Asn Trp Leu Leu Thr Ser Trp Ile Ser Asn	
85 90 95	

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GAA GGT GCT TCC AGA ATC TTC ATA GAA CTC AAA TTT ACC CTG CGG GAC Glu Gly Ala Ser Arg Ile Phe Ile Glu Leu Lys Phe Thr Leu Arg Asp 100 105 110	336
TGC AAC AGC CTT CCT GGA GGA CTG GGG ACC TGT AAG GAA ACC TTT AAT Cys Asn Ser Leu Pro Gly Gly Leu Gly Thr Cys Lys Glu Thr Phe Asn 115 120 125	384
ATG TAT TAC TTT GAG TCA GAT GAT CAG AAT GGG AGA AAC ATC AAG GAA Met Tyr Tyr Phe Glu Ser Asp Asp Gln Asn Gly Arg Asn Ile Lys Glu 130 135 140	432
AAC CAA TAC ATC AAA ATT GAT ACC ATT GCT GCC GAT GAA AGC TTT ACA Asn Gln Tyr Ile Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr 145 150 155 160	480
GAA CTT GAT CTT GGT GAC CGT GTT ATG AAA CTG AAT ACA GAG GTC AGA Glu Leu Asp Leu Gly Asp Arg Val Met Lys Leu Asn Thr Glu Val Arg 165 170 175	528
GAT GTA GGA CCT CTA AGC AAA AAG GGA TTT TAT CTT GCT TTT CAA GAT Asp Val Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp 180 185 190	576
GTT GGT GCT TGC ATT GCT CTG GTT TCT GTG CGT GTA TAC TAT AAA AAA Val Gly Ala Cys Ile Ala Leu Val Ser Val Arg Val Tyr Tyr Lys Lys 195 200 205	624
TGC CCT TCT GTG GTA CGA CAC TTG GCT GTC TTC CCT GAC ACC ATC ACT Cys Pro Ser Val Val Arg His Leu Ala Val Phe Pro Asp Thr Ile Thr 210 215 220	672
GGA GCT GAT TCT TCC CAA TTG CTC GAA GTG TCG GGC TCC TGT GTC AAC Gly Ala Asp Ser Ser Gln Leu Leu Glu Val Ser Gly Ser Cys Val Asn 225 230 235 240	720
CAT TCT GTG ACC GAT GAA CCT CCC AAA ATG CAC TGC AGC GCC GAA GGG His Ser Val Thr Asp Glu Pro Pro Lys Met His Cys Ser Ala Glu Gly 245 250 255	768
GAG TGG CTG GTG CCC ATC GGG AAA TGC ATG TGC AAG GCA GGA TAT GAA Glu Trp Leu Val Pro Ile Gly Lys Cys Met Cys Lys Ala Gly Tyr Glu 260 265 270	816
GAG AAA AAT GGC ACC TGT CAA GTG TGC AGA CCT GGG TTC TTC AAA GCC Glu Lys Asn Gly Thr Cys Gln Val Cys Arg Pro Gly Phe Phe Lys Ala 275 280 285	864
TCA CCT CAC ATC CAG AGC TGC GGC AAA TGT CCA CCT CAC AGT TAT ACC Ser Pro His Ile Gln Ser Cys Gly Lys Cys Pro Pro His Ser Tyr Thr 290 295 300	912
CAT GAG GAA GCT TCA ACC TCT TGT GTC TGT GAA AAG GAT TAT TTC AGG His Glu Glu Ala Ser Thr Ser Cys Val Cys Glu Lys Asp Tyr Phe Arg 305 310 315 320	960

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AGA	GAG	TCT	GAT	CCA	CCC	ACA	ATG	GCA	TGC	ACA	AGA	CCC	CCC	TCT	GCT	1008
Arg	Glu	Ser	Asp	Pro	Pro	Thr	Met	Ala	Cys	Thr	Arg	Pro	Pro	Ser	Ala	
				325					330					335		
CCT	CGG	AAT	GCC	ATC	TCA	AAT	GTT	AAT	GAA	ACT	AGT	GTC	TTT	CTG	GAA	1056
Pro	Arg	Asn	Ala	Ile	Ser	Asn	Val	Asn	Glu	Thr	Ser	Val	Phe	Leu	Glu	
			340					345					350			
TGG	ATT	CCG	CCT	GCT	GAC	ACT	GGT	GGA	AGG	AAA	GAC	GTG	TCA	TAT	TAT	1104
Trp	Ile	Pro	Pro	Ala	Asp	Thr	Gly	Gly	Arg	Lys	Asp	Val	Ser	Tyr	Tyr	
		355					360					365				
ATT	GCA	TGC	AAG	AAG	TGC	AAC	TCC	CAT	GCA	GGT	GTG	TGT	GAG	GAG	TGT	1152
Ile	Ala	Cys	Lys	Lys	Cys	Asn	Ser	His	Ala	Gly	Val	Cys	Glu	Glu	Cys	
	370					375					380					
GGC	GGT	CAT	GTC	AGG	TAC	CTT	CCC	CGG	CAA	AGC	GGC	CTG	AAA	AAC	ACC	1200
Gly	Gly	His	Val	Arg	Tyr	Leu	Pro	Arg	Gln	Ser	Gly	Leu	Lys	Asn	Thr	
385					390					395					400	
TCT	GTC	ATG	ATG	GTG	GAT	CTA	CTC	GCT	CAC	ACA	AAC	TAT	ACC	TTT	GAG	1248
Ser	Val	Met	Met	Val	Asp	Leu	Leu	Ala	His	Thr	Asn	Tyr	Thr	Phe	Glu	
				405				410						415		
ATT	GAG	GCA	GTG	AAT	GGA	GTG	TCC	GAC	TTG	AGC	CCA	GGA	GCC	CGG	CAG	1296
Ile	Glu	Ala	Val	Asn	Gly	Val	Ser	Asp	Leu	Ser	Pro	Gly	Ala	Arg	Gln	
			420					425					430			
TAT	GTG	TCT	GTA	AAT	GTA	ACC	ACA	AAT	CAA	GCA	GCT	CCA	TCT	CCA	GTC	1344
Tyr	Val	Ser	Val	Asn	Val	Thr	Thr	Asn	Gln	Ala	Ala	Pro	Ser	Pro	Val	
			435				440					445				
ACC	AAT	GTG	AAA	AAA	GGG	AAA	ATT	GCA	AAA	AAC	AGC	ATC	TCT	TTG	TCT	1392
Thr	Asn	Val	Lys	Lys	Gly	Lys	Ile	Ala	Lys	Asn	Ser	Ile	Ser	Leu	Ser	
	450					455					460					
TGG	CAA	GAA	CCA	GAT	CGT	CCC	AAT	GGA	ATC	ATC	CTA	GAG	TAT	GAA	ATC	1440
Trp	Gln	Glu	Pro	Asp	Arg	Pro	Asn	Gly	Ile	Ile	Leu	Glu	Tyr	Glu	Ile	
	465				470				475					480		
AAG	CAT	TTT	GAA	AAG	GAC	CAA	GAG	ACC	AGC	TAC	ACG	ATT	ATC	AAA	TCT	1488
Lys	His	Phe	Glu	Lys	Asp	Gln	Glu	Thr	Ser	Tyr	Thr	Ile	Ile	Lys	Ser	
				485				490						495		
AAA	GAG	ACA	ACT	ATT	ACT	GCA	GAG	GGC	TTG	AAA	CCA	GCT	TCA	GTT	TAT	1536
Lys	Glu	Thr	Thr	Ile	Thr	Ala	Glu	Gly	Leu	Lys	Pro	Ala	Ser	Val	Tyr	
			500					505					510			
GTC	TTC	CAA	ATT	CGA	GCA	CGT	ACA	GCA	GCA	GGC	TAT	GGT	GTC	TTC	AGT	1584
Val	Phe	Gln	Ile	Arg	Ala	Arg	Thr	Ala	Ala	Gly	Tyr	Gly	Val	Phe	Ser	
			515				520					525				
CGA	AGA	TTT	GAG	TTT	GAA	ACC	ACC	CCA	GTG	TTT	GCA	GCA	TCC	AGC	GAT	1632
Arg	Arg	Phe	Glu	Phe	Glu	Thr	Thr	Pro	Val	Phe	Ala	Ala	Ser	Ser	Asp	
			530			535					540					

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CAA AGC CAG ATT CCT GTA ATT GCT GTG TCT GTG ACA GTA GGA GTC ATT Gln Ser Gln Ile Pro Val Ile Ala Val Ser Val Thr Val Gly Val Ile 545 550 555 560	1680
TTG TTG GCA GTG GTT ATC GGC GTC CTC CTC AGT GGA AGG CGG TGT GGC Leu Leu Ala Val Val Ile Gly Val Leu Leu Ser Gly Arg Arg Cys Gly 565 570 575	1728
TAC AGC AAA GCA AAA CAA GAT CCA GAA GAG GAA AAG ATG CAT TTT CAT Tyr Ser Lys Ala Lys Gln Asp Pro Glu Glu Lys Met His Phe His 580 585 590	1776
AAT GGG CAC ATT AAA CTG CCA GGA GTA AGA ACT TAC ATT GAT CCA CAT Asn Gly His Ile Lys Leu Pro Gly Val Arg Thr Tyr Ile Asp Pro His 595 600 605	1824
ACC TAT GAG GAT CCC AAT CAA GCT GTC CAC GAA TTT GCC AAG GAG ATA Thr Tyr Glu Asp Pro Asn Gln Ala Val His Glu Phe Ala Lys Glu Ile 610 615 620	1872
GAA GCA TCA TGT ATC ACC ATT GAG AGA GTT ATT GGA GCA GGT GAA TTT Glu Ala Ser Cys Ile Thr Ile Glu Arg Val Ile Gly Ala Gly Glu Phe 625 630 635 640	1920
GGT GAA GTT TGT AGT GGA CGT TTG AAA CTA CCA GGA AAA AGA GAA TTA Gly Glu Val Cys Ser Gly Arg Leu Lys Leu Pro Gly Lys Arg Glu Leu 645 650 655	1968
CCT GTG GCT ATC AAA ACC CTT AAA GTA GGC TAT ACT GAA AAG CAA CGC Pro Val Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr Glu Lys Gln Arg 660 665 670	2016
AGA GAT TTC CTA GGT GAA GCA AGT ATC ATG GGA CAG TTT GAT CAT CCT Arg Asp Phe Leu Gly Glu Ala Ser Ile Met Gly Gln Phe Asp His Pro 675 680 685	2064
AAC ATC ATC CAT TTA GAA GGT GTG GTG ACC AAA AGT AAA CCA GTG ATG Asn Ile Ile His Leu Glu Gly Val Val Thr Lys Ser Lys Pro Val Met 690 695 700	2112
ATC GTG ACA GAG TAT ATG GAG AAT GGC TCT TTA GAT ACA TTT TTG AAG Ile Val Thr Glu Tyr Met Glu Asn Gly Ser Leu Asp Thr Phe Leu Lys 705 710 715 720	2160
AAA AAC GAT GGG CAG TTC ACT GTG ATT CAG CTT GTT GGC ATG CTG AGA Lys Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val Gly Met Leu Arg 725 730 735	2208
GGT ATC TCT GCA GGA ATG AAG TAC CTT TCT GAC ATG GGC TAT GTG CAT Gly Ile Ser Ala Gly Met Lys Tyr Leu Ser Asp Met Gly Tyr Val His 740 745 750	2256
AGA GAT CTT GCT GCC AGA AAC ATC TTA ATC AAC AGT AAC CTT GTG TGC Arg Asp Leu Ala Ala Arg Asn Ile Leu Ile Asn Ser Asn Leu Val Cys 755 760 765	2304

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AAA GTG TCT GAC TTT GGA CTT TCC CGG GTA CTG GAA GAT GAT CCC GAG	2352
Lys Val Ser Asp Phe Gly Leu Ser Arg Val Leu Glu Asp Asp Pro Glu	
770 775 780	
GCA GCC TAC ACC ACA AGG GGA GGA AAA ATT CCA ATC AGA TGG ACT GCC	2400
Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala	
785 790 795 800	
CCA GAA GCA ATA GCT TTC CGA AAG TTT ACT TCT GGC AGT GAT GTC TGG	2448
Pro Glu Ala Ile Ala Phe Arg Lys Phe Thr Ser Ala Ser Asp Val Trp	
805 810 815	
AGT TAT GGA ATA GTA ATG TGG GAA GTT GTG TCT TAT GGA GAG AGA CCC	2496
Ser Tyr Gly Ile Val Met Trp Glu Val Val Ser Tyr Gly Glu Arg Pro	
820 825 830	
TAC TGG GAG ATG ACC AAT CAA GAT GTG ATT AAA GCG GTA GAG GAA GGC	2544
Tyr Trp Glu Met Thr Asn Gln Asp Val Ile Lys Ala Val Glu Glu Gly	
835 840 845	
TAT CGT CTG CCA AGC CCC ATG GAT TGT CCT GCT GCT CTC TAT CAG TTA	2592
Tyr Arg Leu Pro Ser Pro Met Asp Cys Pro Ala Ala Leu Tyr Gln Leu	
850 855 860	
ATG CTG GAT TGC TGG CAG AAA GAG CGA AAT AGC AGG CCC AAG TTT GAT	2640
Met Leu Asp Cys Trp Gln Lys Glu Arg Asn Ser Arg Pro Lys Phe Asp	
865 870 875 880	
GAA ATA GTC AAC ATG TTG GAC AAG CTG ATA CGT AAC CCA AGT AGT CTG	2688
Glu Ile Val Asn Met Leu Asp Lys Leu Ile Arg Asn Pro Ser Ser Leu	
885 890 895	
AAG ACG CTG GTT AAT GCA TCC TGC AGA GTA TCT AAT TTA TTG GCA GAA	2736
Lys Thr Leu Val Asn Ala Ser Cys Arg Val Ser Asn Leu Leu Ala Glu	
900 905 910	
CAT AGC CCA CTA GGA TCT GGG GCC TAC AGA TCA GTA GGT GAA TGG CTA	2784
His Ser Pro Leu Gly Ser Gly Ala Tyr Arg Ser Val Gly Glu Trp Leu	
915 920 925	
GAG GCA ATC AAG ATG GGC CGG TAT ACA GAG ATT TTC ATG GAA AAT GGA	2832
Glu Ala Ile Lys Met Gly Arg Tyr Thr Glu Ile Phe Met Glu Asn Gly	
930 935 940	
TAC AGT TCA ATG GAC GCT GTG GCT CAG GTG ACC TTG GAG GAT TTG AGA	2880
Tyr Ser Ser Met Asp Ala Val Ala Gln Val Thr Leu Glu Asp Leu Arg	
945 950 955 960	
CGG CTT GGA GTG ACT CTT GTC GGT CAC CAG AAG AAG ATC ATG AAC AGC	2928
Arg Leu Gly Val Thr Leu Val Gly His Gln Lys Lys Ile Met Asn Ser	
965 970 975	
CTT CAA GAA ATG AAG GTG CAG CTG GTA AAC GGA ATG GTG CCA TTG TAACTTCATG	2983
Leu Gln Glu Met Lys Val Gln Leu Val Asn Gly Met Val Pro Leu	
980 985 990	
TAAATGTCGC TTCTTCAAGT GAATGATTCT GCACTTTGTA AACAGCACTG AGATTTATTT	3043

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TAACAAAAAA AGGGGGAAAA GGGAAAACAG TGATTCTAA ACCTTAGAAA ACATTGCGCT 3103
 CAGCCACAGA ATTTGTAATC ATGGTTTTAC TGAAGTATCC AGTTCTTAGT CCTTAGTCT 3162

(2) INFORMATION FOR SEQ ID NO:13:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 991 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Pro Ala Ser Leu Ala Gly Cys Tyr Ser Ala Pro Arg Arg Ala Pro Leu
 1 5 10 15
 Trp Thr Cys Leu Leu Leu Cys Ala Ala Leu Arg Thr Leu Leu Ala Ser
 20 25 30
 Pro Ser Asn Glu Val Asn Leu Leu Asp Ser Arg Thr Val Met Gly Asp
 35 40 45
 Leu Gly Trp Ile Ala Phe Pro Lys Asn Gly Trp Glu Glu Ile Gly Glu
 50 55 60
 Val Asp Glu Asn Tyr Ala Pro Ile His Thr Tyr Gln Val Cys Lys Val
 65 70 75 80
 Met Glu Gln Asn Gln Asn Asn Trp Leu Leu Thr Ser Trp Ile Ser Asn
 85 90 95
 Glu Gly Ala Ser Arg Ile Phe Ile Glu Leu Lys Phe Thr Leu Arg Asp
 100 105 110
 Cys Asn Ser Leu Pro Gly Gly Leu Gly Thr Cys Lys Glu Thr Phe Asn
 115 120 125
 Met Tyr Tyr Phe Glu Ser Asp Asp Gln Asn Gly Arg Asn Ile Lys Glu
 130 135 140
 Asn Gln Tyr Ile Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr
 145 150 155 160
 Glu Leu Asp Leu Gly Asp Arg Val Met Lys Leu Asn Thr Glu Val Arg
 165 170 175
 Asp Val Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp
 180 185 190
 Val Gly Ala Cys Ile Ala Leu Val Ser Val Arg Val Tyr Tyr Lys Lys
 195 200 205
 Cys Pro Ser Val Val Arg His Leu Ala Val Phe Pro Asp Thr Ile Thr
 210 215 220

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Gly Ala Asp Ser Ser Gln Leu Leu Glu Val Ser Gly Ser Cys Val Asn
 225 230 235 240
 His Ser Val Thr Asp Glu Pro Pro Lys Met His Cys Ser Ala Glu Gly
 245 250 255
 Glu Trp Leu Val Pro Ile Gly Lys Cys Met Cys Lys Ala Gly Tyr Glu
 260 265 270
 Glu Lys Asn Gly Thr Cys Gln Val Cys Arg Pro Gly Phe Phe Lys Ala
 275 280 285
 Ser Pro His Ile Gln Ser Cys Gly Lys Cys Pro Pro His Ser Tyr Thr
 290 295 300
 His Glu Glu Ala Ser Thr Ser Cys Val Cys Glu Lys Asp Tyr Phe Arg
 305 310 315 320
 Arg Glu Ser Asp Pro Pro Thr Met Ala Cys Thr Arg Pro Pro Ser Ala
 325 330 335
 Pro Arg Asn Ala Ile Ser Asn Val Asn Glu Thr Ser Val Phe Leu Glu
 340 345 350
 Trp Ile Pro Pro Ala Asp Thr Gly Gly Arg Lys Asp Val Ser Tyr Tyr
 355 360 365
 Ile Ala Cys Lys Lys Cys Asn Ser His Ala Gly Val Cys Glu Glu Cys
 370 375 380
 Gly Gly His Val Arg Tyr Leu Pro Arg Gln Ser Gly Leu Lys Asn Thr
 385 390 395 400
 Ser Val Met Met Val Asp Leu Leu Ala His Thr Asn Tyr Thr Phe Glu
 405 410 415
 Ile Glu Ala Val Asn Gly Val Ser Asp Leu Ser Pro Gly Ala Arg Gln
 420 425 430
 Tyr Val Ser Val Asn Val Thr Thr Asn Gln Ala Ala Pro Ser Pro Val
 435 440 445
 Thr Asn Val Lys Lys Gly Lys Ile Ala Lys Asn Ser Ile Ser Leu Ser
 450 455 460
 Trp Gln Glu Pro Asp Arg Pro Asn Gly Ile Ile Leu Glu Tyr Glu Ile
 465 470 475 480
 Lys His Phe Glu Lys Asp Gln Glu Thr Ser Tyr Thr Ile Ile Lys Ser
 485 490 495
 Lys Glu Thr Thr Ile Thr Ala Glu Gly Leu Lys Pro Ala Ser Val Tyr
 500 505 510
 Val Phe Gln Ile Arg Ala Arg Thr Ala Ala Gly Tyr Gly Val Phe Ser
 515 520 525

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Arg Arg Phe Glu Phe Glu Thr Thr Pro Val Phe Ala Ala Ser Ser Asp
 530 535 540
 Gln Ser Gln Ile Pro Val Ile Ala Val Ser Val Thr Val Gly Val Ile
 545 550 555 560
 Leu Leu Ala Val Val Ile Gly Val Leu Leu Ser Gly Arg Arg Cys Gly
 565 570 575
 Tyr Ser Lys Ala Lys Gln Asp Pro Glu Glu Glu Lys Met His Phe His
 580 585 590
 Asn Gly His Ile Lys Leu Pro Gly Val Arg Thr Tyr Ile Asp Pro His
 595 600 605
 Thr Tyr Glu Asp Pro Asn Gln Ala Val His Glu Phe Ala Lys Glu Ile
 610 615 620
 Glu Ala Ser Cys Ile Thr Ile Glu Arg Val Ile Gly Ala Gly Glu Phe
 625 630 635 640
 Gly Glu Val Cys Ser Gly Arg Leu Lys Leu Pro Gly Lys Arg Glu Leu
 645 650 655
 Pro Val Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr Glu Lys Gln Arg
 660 665 670
 Arg Asp Phe Leu Gly Glu Ala Ser Ile Met Gly Gln Phe Asp His Pro
 675 680 685
 Asn Ile Ile His Leu Glu Gly Val Val Thr Lys Ser Lys Pro Val Met
 690 695 700
 Ile Val Thr Glu Tyr Met Glu Asn Gly Ser Leu Asp Thr Phe Leu Lys
 705 710 715 720
 Lys Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val Gly Met Leu Arg
 725 730 735
 Gly Ile Ser Ala Gly Met Lys Tyr Leu Ser Asp Met Gly Tyr Val His
 740 745 750
 Arg Asp Leu Ala Ala Arg Asn Ile Leu Ile Asn Ser Asn Leu Val Cys
 755 760 765
 Lys Val Ser Asp Phe Gly Leu Ser Arg Val Leu Glu Asp Asp Pro Glu
 770 775 780
 Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala
 785 790 795 800
 Pro Glu Ala Ile Ala Phe Arg Lys Phe Thr Ser Ala Ser Asp Val Trp
 805 810 815
 Ser Tyr Gly Ile Val Met Trp Glu Val Val Ser Tyr Gly Glu Arg Pro
 820 825 830

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Tyr Trp Glu Met Thr Asn Gln Asp Val Ile Lys Ala Val Glu Glu Gly
 835 840 845
 Tyr Arg Leu Pro Ser Pro Met Asp Cys Pro Ala Ala Leu Tyr Gln Leu
 850 855 860
 Met Leu Asp Cys Trp Gln Lys Glu Arg Asn Ser Arg Pro Lys Phe Asp
 865 870 875 880
 Glu Ile Val Asn Met Leu Asp Lys Leu Ile Arg Asn Pro Ser Ser Leu
 885 890 895
 Lys Thr Leu Val Asn Ala Ser Cys Arg Val Ser Asn Leu Leu Ala Glu
 900 905 910
 His Ser Pro Leu Gly Ser Gly Ala Tyr Arg Ser Val Gly Glu Trp Leu
 915 920 925
 Glu Ala Ile Lys Met Gly Arg Tyr Thr Glu Ile Phe Met Glu Asn Gly
 930 935 940
 Tyr Ser Ser Met Asp Ala Val Ala Gln Val Thr Leu Glu Asp Leu Arg
 945 950 955 960
 Arg Leu Gly Val Thr Leu Val Gly His Gln Lys Lys Ile Met Asn Ser
 965 970 975
 Leu Gln Glu Met Lys Val Gln Leu Val Asn Gly Met Val Pro Leu
 980 985 990

(2) INFORMATION FOR SEQ ID NO:14:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 3116 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 34..2994

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

AAGCGGCAGG AGCAGCGTTG GCACCGGCGA ACC ATG GCT GGG ATT TTC TAT TTC
 Met Ala Gly Ile Phe Tyr Phe
 1 5

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GCC CTA TTT TCG TGT CTC TTC GGG ATT TGC GAC GCT GTC ACA GGT TCC
 Ala Leu Phe Ser Cys Leu Phe Gly Ile Cys Asp Ala Val Thr Gly Ser
 10 15 20

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AGG GTA TAC CCC GCG AAT GAA GTT ACC TTA TTG GAT TCC AGA TCT GTT Arg Val Tyr Pro Ala Asn Glu Val Thr Leu Leu Asp Ser Arg Ser Val 25 30 35	150
CAG GGA GAA CTT GGG TGG ATA GCA AGC CCT CTG GAA GGA GGG TGG GAG Gln Gly Glu Leu Gly Trp Ile Ala Ser Pro Leu Glu Gly Gly Trp Glu 40 45 50 55	198
GAA GTG AGT ATC ATG GAT GAA AAA AAT ACA CCA ATC CGA ACC TAC CAA Glu Val Ser Ile Met Asp Glu Lys Asn Thr Pro Ile Arg Thr Tyr Gln 60 65 70	246
GTG TGC AAT GTG ATG GAA CCC AGC CAG AAT AAC TGG CTA CGA ACT GAT Val Cys Asn Val Met Glu Pro Ser Gln Asn Asn Trp Leu Arg Thr Asp 75 80 85	294
TGG ATC ACC CGA GAA GGG GCT CAG AGG GTG TAT ATT GAG ATT AAA TTC Trp Ile Thr Arg Glu Gly Ala Gln Arg Val Tyr Ile Glu Ile Lys Phe 90 95 100	342
ACC TTG AGG GAC TGC AAT AGT CTT CCG GGC GTC ATG GGG ACT TGC AAG Thr Leu Arg Asp Cys Asn Ser Leu Pro Gly Val Met Gly Thr Cys Lys 105 110 115	390
GAG ACG TTT AAC CTG TAC TAC TAT GAA TCA GAC AAC GAC AAA GAG CGT Glu Thr Phe Asn Leu Tyr Tyr Tyr Glu Ser Asp Asn Asp Lys Glu Arg 120 125 130 135	438
TTC ATC AGA GAG AAC CAG TTT GTC AAA ATT GAC ACC ATT GCT GCT GAT Phe Ile Arg Glu Asn Gln Phe Val Lys Ile Asp Thr Ile Ala Ala Asp 140 145 150	486
GAG AGC TTC ACC CAA GTG GAC ATT GGT GAC AGA ATC ATG AAG CTG AAC Glu Ser Phe Thr Gln Val Asp Ile Gly Asp Arg Ile Met Lys Leu Asn 155 160 165	534
ACC GAG ATC CGG GAT GTA GGG CCA TTA AGC AAA AAG GGG TTT TAC CTG Thr Glu Ile Arg Asp Val Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu 170 175 180	582
GCT TTT CAG GAT GTG GGG GCC TGC ATC GCC CTG GTA TCA GTC CGT GTG Ala Phe Gln Asp Val Gly Ala Cys Ile Ala Leu Val Ser Val Arg Val 185 190 195	630
TTC TAT AAA AAG TGT CCA CTC ACA GTC CGC AAT CTG GCC CAG TTT CCT Phe Tyr Lys Lys Cys Pro Leu Thr Val Arg Asn Leu Ala Gln Phe Pro 200 205 210 215	678
GAC ACC ATC ACA GGG GCT GAT ACG TCT TCC CTG GTG GAA GTT CGA GGC Asp Thr Ile Thr Gly Ala Asp Thr Ser Ser Leu Val Glu Val Arg Gly 220 225 230	726
TCC TGT GTC AAC AAC TCA GAA GAG AAA GAT GTG CCA AAA ATG TAC TGT Ser Cys Val Asn Asn Ser Glu Glu Lys Asp Val Pro Lys Met Tyr Cys 235 240 245	774

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GGG GCA GAT GGT GAA TGG CTG GTA CCC ATT GGC AAC TGC CTA TGC AAC	822
Gly Ala Asp Gly Glu Trp Leu Val Pro Ile Gly Asn Cys Leu Cys Asn	
250 255 260	
GCT GGG CAT GAG GAG CGG AGC GGA GAA TGC CAA GCT TGC AAA ATT GGA	870
Ala Gly His Glu Glu Arg Ser Gly Glu Cys Gln Ala Cys Lys Ile Gly	
265 270 275	
TAT TAC AAG GCT CTC TCC ACG GAT GCC ACC TGT GCC AAG TGC CCA CCC	918
Tyr Tyr Lys Ala Leu Ser Thr Asp Ala Thr Cys Ala Lys Cys Pro Pro	
280 285 290 295	
CAC AGC TAC TCT GTC TGG GAA GGA GCC ACC TCG TGC ACC TGT GAC CGA	966
His Ser Tyr Ser Val Trp Glu Gly Ala Thr Ser Cys Thr Cys Asp Arg	
300 305 310	
GGC TTT TTC AGA GCT GAC AAC GAT GCT GCC TCT ATG CCC TGC ACC CGT	1014
Gly Phe Phe Arg Ala Asp Asn Asp Ala Ala Ser Met Pro Cys Thr Arg	
315 320 325	
CCA CCA TCT GCT CCC CTG AAC TTG ATT TCA AAT GTC AAC GAG ACA TCT	1062
Pro Pro Ser Ala Pro Leu Asn Leu Ile Ser Asn Val Asn Glu Thr Ser	
330 335 340	
GTG AAC TTG GAA TGG AGT AGC CCT CAG AAT ACA GGT GGC CGC CAG GAC	1110
Val Asn Leu Glu Trp Ser Ser Pro Gln Asn Thr Gly Gly Arg Gln Asp	
345 350 355	
ATT TCC TAT AAT GTG GTA TGC AAG AAA TGT GGA GCT GGT GAC CCC AGC	1158
Ile Ser Tyr Asn Val Val Cys Lys Lys Cys Gly Ala Gly Asp Pro Ser	
360 365 370 375	
AAG TGC CGA CCC TGT GGA AGT GGG GTC CAC TAC ACC CCA CAG CAG AAT	1206
Lys Cys Arg Pro Cys Gly Ser Gly Val His Tyr Thr Pro Gln Gln Asn	
380 385 390	
GGC TTG AAG ACC ACC AAA GTC TCC ATC ACT GAC CTC CTA GCT CAT ACC	1254
Gly Leu Lys Thr Thr Lys Val Ser Ile Thr Asp Leu Leu Ala His Thr	
395 400 405	
AAT TAC ACC TTT GAA ATC TGG GCT GTG AAT GGA GTG TCC AAA TAT AAC	1302
Asn Tyr Thr Phe Glu Ile Trp Ala Val Asn Gly Val Ser Lys Tyr Asn	
410 415 420	
CCT AAC CCA GAC CAA TCA GTT TCT GTC ACT GTG ACC ACC AAC CAA GCA	1350
Pro Asn Pro Asp Gln Ser Val Ser Val Thr Val Thr Asn Gln Ala	
425 430 435	
GCA CCA TCA TCC ATT GCT TTG GTC CAG GCT AAA GAA GTC ACA AGA TAC	1398
Ala Pro Ser Ser Ile Ala Leu Val Gln Ala Lys Glu Val Thr Arg Tyr	
440 445 450 455	
AGT GTG GCA CTG GCT TGG CTG GAA CCA GAT CGG CCC AAT GGG GTA ATC	1446
Ser Val Ala Leu Ala Trp Leu Glu Pro Asp Arg Pro Asn Gly Val Ile	
460 465 470	

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CTG GAA TAT GAA GTC AAG TAT TAT GAG AAG GAT CAG AAT GAG CGA AGC Leu Glu Tyr Glu Val Lys Tyr Tyr Glu Lys Asp Gln Asn Glu Arg Ser 475 480 485	1494
TAT CGT ATA GTT CGG ACA GCT GCC AGG AAC ACA GAT ATC AAA GGC CTG Tyr Arg Ile Val Arg Thr Ala Ala Arg Asn Thr Asp Ile Lys Gly Leu 490 495 500	1542
AAC CCT CTC ACT TCC TAT GTT TTC CAC GTG CGA GCC AGG ACA GCA GCT Asn Pro Leu Thr Ser Tyr Val Phe His Val Arg Ala Arg Thr Ala Ala 505 510 515	1590
GGC TAT GGA GAC TTC AGT GAG CCC TTG GAG GTT ACA ACC AAC ACA GTG Gly Tyr Gly Asp Phe Ser Glu Pro Leu Glu Val Thr Thr Asn Thr Val 520 525 530 535	1638
CCT TCC CGG ATC ATT GGA GAT GGG GCT AAC TCC ACA GTC CTT CTG GTC Pro Ser Arg Ile Ile Gly Asp Gly Ala Asn Ser Thr Val Leu Leu Val 540 545 550	1686
TCT GTC TCG GGC AGT GTG GTG CTG GTG GTA ATT CTC ATT GCA GCT TTT Ser Val Ser Gly Ser Val Val Leu Val Val Ile Leu Ile Ala Ala Phe 555 560 565	1734
GTC ATC AGC CGG AGA CGG AGT AAA TAC AGT AAA GCC AAA CAA GAA GCG Val Ile Ser Arg Arg Arg Ser Lys Tyr Ser Lys Ala Lys Gln Glu Ala 570 575 580	1782
GAT GAA GAG AAA CAT TTG AAT CAA GGT GTA AGA ACA TAT GTG GAC CCC Asp Glu Glu Lys His Leu Asn Gln Gly Val Arg Thr Tyr Val Asp Pro 585 590 595	1830
TTT ACG TAC GAA GAT CCC AAC CAA GCA GTG CGA GAG TTT GCC AAA GAA Phe Thr Tyr Glu Asp Pro Asn Gln Ala Val Arg Glu Phe Ala Lys Glu 600 605 610 615	1878
ATT GAC GCA TCC TGC ATT AAG ATT GAA AAA GTT ATA GGA GTT GGT GAA Ile Asp Ala Ser Cys Ile Lys Ile Glu Lys Val Ile Gly Val Gly Glu 620 625 630	1926
TTT GGT GAG GTA TGC AGT GGG CGT CTC AAA GTG CCT GGC AAG AGA GAG Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Val Pro Gly Lys Arg Glu 635 640 645	1974
ATC TGT GTG GCT ATC AAG ACT CTG AAA GCT GGT TAT ACA GAC AAA CAG Ile Cys Val Ala Ile Lys Thr Leu Lys Ala Gly Tyr Thr Asp Lys Gln 650 655 660	2022
AGG AGA GAC TTC CTG AGT GAG GCC AGC ATC ATG GGA CAG TTT GAC CAT Arg Arg Asp Phe Leu Ser Glu Ala Ser Ile Met Gly Gln Phe Asp His 665 670 675	2070
CCG AAC ATC ATT CAC TTG GAA GGC GTG GTC ACT AAA TGT AAA CCA GTA Pro Asn Ile Ile His Leu Glu Gly Val Val Thr Lys Cys Lys Pro Val 680 685 690 695	2118

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ATG	ATC	ATA	ACA	GAG	TAC	ATG	GAG	AAT	GGC	TCC	TTG	GAT	GCA	TTC	CTC	2166
Met	Ile	Ile	Thr	Glu	Tyr	Met	Glu	Asn	Gly	Ser	Leu	Asp	Ala	Phe	Leu	
				700					705					710		
AGG	AAA	AAT	GAT	GGC	AGA	TTT	ACA	GTC	ATT	CAG	CTG	GTG	GGC	ATG	CTT	2214
Arg	Lys	Asn	Asp	Gly	Arg	Phe	Thr	Val	Ile	Gln	Leu	Val	Gly	Met	Leu	
			715					720					725			
CGT	GGC	ATT	GGG	TCT	GGG	ATG	AAG	TAT	TTA	TCT	GAT	ATG	AGC	TAT	GTG	2262
Arg	Gly	Ile	Gly	Ser	Gly	Met	Lys	Tyr	Leu	Ser	Asp	Met	Ser	Tyr	Val	
			730				735					740				
CAT	CGT	GAT	CTG	GCC	GCA	CGG	AAC	ATC	CTG	GTG	AAC	AGC	AAC	TTG	GTC	2310
His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Val	Asn	Ser	Asn	Leu	Val	
	745					750					755					
TGC	AAA	GTG	TCT	GAT	TTT	GGC	ATG	TCC	CGA	GTG	CTT	GAG	GAT	GAT	CCG	2358
Cys	Lys	Val	Ser	Asp	Phe	Gly	Met	Ser	Arg	Val	Leu	Glu	Asp	Asp	Pro	
760					765					770					775	
GAA	GCA	GCT	TAC	ACC	ACC	AGG	GGT	GGC	AAG	ATT	CCT	ATC	CGG	TGG	ACT	2406
Glu	Ala	Ala	Tyr	Thr	Thr	Arg	Gly	Gly	Lys	Ile	Pro	Ile	Arg	Trp	Thr	
				780					785					790		
GCG	CCA	GAA	GCA	ATT	GCC	TAT	CGT	AAA	TTC	ACA	TCA	GCA	AGT	GAT	GTA	2454
Ala	Pro	Glu	Ala	Ile	Ala	Tyr	Arg	Lys	Phe	Thr	Ser	Ala	Ser	Asp	Val	
			795					800					805			
TGG	AGC	TAT	GGA	ATC	GTT	ATG	TGG	GAA	GTG	ATG	TCG	TAC	GGG	GAG	AGG	2502
Trp	Ser	Tyr	Gly	Ile	Val	Met	Trp	Glu	Val	Met	Ser	Tyr	Gly	Glu	Arg	
		810					815					820				
CCC	TAT	TGG	GAT	ATG	TCC	AAT	CAA	GAT	GTG	ATT	AAA	GCC	ATT	GAG	GAA	2550
Pro	Tyr	Trp	Asp	Met	Ser	Asn	Gln	Asp	Val	Ile	Lys	Ala	Ile	Glu	Glu	
	825					830					835					
GGC	TAT	CGG	TTA	CCC	CCT	CCA	ATG	GAC	TGC	CCC	ATT	GCG	CTC	CAC	CAG	2598
Gly	Tyr	Arg	Leu	Pro	Pro	Pro	Met	Asp	Cys	Pro	Ile	Ala	Leu	His	Gln	
840					845					850					855	
CTG	ATG	CTA	GAC	TGC	TGG	CAG	AAG	GAG	AGG	AGC	GAC	AGG	CCT	AAA	TTT	2646
Leu	Met	Leu	Asp	Cys	Trp	Gln	Lys	Glu	Arg	Ser	Asp	Arg	Pro	Lys	Phe	
				860					865					870		
GGG	CAG	ATT	GTC	AAC	ATG	TTG	GAC	AAA	CTC	ATC	CGC	AAC	CCC	AAC	AGC	2694
Gly	Gln	Ile	Val	Asn	Met	Leu	Asp	Lys	Leu	Ile	Arg	Asn	Pro	Asn	Ser	
			875					880					885			
TTG	AAG	AGG	ACA	GGG	ACG	GAG	AGC	TCC	AGA	CCT	AAC	ACT	GCC	TTG	TTG	2742
Leu	Lys	Arg	Thr	Gly	Thr	Glu	Ser	Ser	Arg	Pro	Asn	Thr	Ala	Leu	Leu	
			890				895					900				
GAT	CCA	AGC	TCC	CCT	GAA	TTC	TCT	GCT	GTG	GTA	TCA	GTG	GGC	GAT	TGG	2790
Asp	Pro	Ser	Ser	Pro	Glu	Phe	Ser	Ala	Val	Val	Ser	Val	Gly	Asp	Trp	
	905					910						915				

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CTC CAG GCC ATT AAA ATG GAC CGG TAT AAG GAT AAC TTC ACA GCT GCT 2838
 Leu Gln Ala Ile Lys Met Asp Arg Tyr Lys Asp Asn Phe Thr Ala Ala
 920 925 930 935

GGT TAT ACC ACA CTA GAG GCT GTG GTG CAC GTG AAC CAG GAG GAC CTG 2886
 Gly Tyr Thr Thr Leu Glu Ala Val Val His Val Asn Gln Glu Asp Leu
 940 945 950

GCA AGA ATT GGT ATC ACA GCC ATC ACG CAC CAG AAT AAG ATT TTG AGC 2934
 Ala Arg Ile Gly Ile Thr Ala Ile Thr His Gln Asn Lys Ile Leu Ser
 955 960 965

AGT GTC CAG GCA ATG CGA ACC CAA ATG CAG CAG ATG CAC GGC AGA ATG 2982
 Ser Val Gln Ala Met Arg Thr Gln Met Gln Gln Met His Gly Arg Met
 970 975 980

GTT CCC GTC TGAGCCAGTA CTGAATAAAC TCAAACTCT TGAAATTAGT 3031
 Val Pro Val
 985

TTACCTCATC CATGCACTTT AATTGAAGAA CTGCACTTTT TTTACTTCGT CTTCGCCCTC 3091

TGAAATTAAA GAAATGAAAA AAAAA 3116

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 986 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Met Ala Gly Ile Phe Tyr Phe Ala Leu Phe Ser Cys Leu Phe Gly Ile
 1 5 10 15

Cys Asp Ala Val Thr Gly Ser Arg Val Tyr Pro Ala Asn Glu Val Thr
 20 25 30

Leu Leu Asp Ser Arg Ser Val Gln Gly Glu Leu Gly Trp Ile Ala Ser
 35 40 45

Pro Leu Glu Gly Gly Trp Glu Glu Val Ser Ile Met Asp Glu Lys Asn
 50 55 60

Thr Pro Ile Arg Thr Tyr Gln Val Cys Asn Val Met Glu Pro Ser Gln
 65 70 75 80

Asn Asn Trp Leu Arg Thr Asp Trp Ile Thr Arg Glu Gly Ala Gln Arg
 85 90 95

Val Tyr Ile Glu Ile Lys Phe Thr Leu Arg Asp Cys Asn Ser Leu Pro
 100 105 110

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Gly Val Met Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Tyr Glu
 115 120 125
 Ser Asp Asn Asp Lys Glu Arg Phe Ile Arg Glu Asn Gln Phe Val Lys
 130 135 140
 Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Val Asp Ile Gly
 145 150 155 160
 Asp Arg Ile Met Lys Leu Asn Thr Glu Ile Arg Asp Val Gly Pro Leu
 165 170 175
 Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Ile
 180 185 190
 Ala Leu Val Ser Val Arg Val Phe Tyr Lys Lys Cys Pro Leu Thr Val
 195 200 205
 Arg Asn Leu Ala Gln Phe Pro Asp Thr Ile Thr Gly Ala Asp Thr Ser
 210 215 220
 Ser Leu Val Glu Val Arg Gly Ser Cys Val Asn Asn Ser Glu Glu Lys
 225 230 235 240
 Asp Val Pro Lys Met Tyr Cys Gly Ala Asp Gly Glu Trp Leu Val Pro
 245 250 255
 Ile Gly Asn Cys Leu Cys Asn Ala Gly His Glu Glu Arg Ser Gly Glu
 260 265 270
 Cys Gln Ala Cys Lys Ile Gly Tyr Tyr Lys Ala Leu Ser Thr Asp Ala
 275 280 285
 Thr Cys Ala Lys Cys Pro Pro His Ser Tyr Ser Val Trp Glu Gly Ala
 290 295 300
 Thr Ser Cys Thr Cys Asp Arg Gly Phe Phe Arg Ala Asp Asn Asp Ala
 305 310 315 320
 Ala Ser Met Pro Cys Thr Arg Pro Pro Ser Ala Pro Leu Asn Leu Ile
 325 330 335
 Ser Asn Val Asn Glu Thr Ser Val Asn Leu Glu Trp Ser Ser Pro Gln
 340 345 350
 Asn Thr Gly Gly Arg Gln Asp Ile Ser Tyr Asn Val Val Cys Lys Lys
 355 360 365
 Cys Gly Ala Gly Asp Pro Ser Lys Cys Arg Pro Cys Gly Ser Gly Val
 370 375 380
 His Tyr Thr Pro Gln Gln Asn Gly Leu Lys Thr Thr Lys Val Ser Ile
 385 390 395 400
 Thr Asp Leu Leu Ala His Thr Asn Tyr Thr Phe Glu Ile Trp Ala Val
 405 410 415

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Asn Gly Val Ser Lys Tyr Asn Pro Asn Pro Asp Gln Ser Val Ser Val
 420 425 430
 Thr Val Thr Thr Asn Gln Ala Ala Pro Ser Ser Ile Ala Leu Val Gln
 435 440 445
 Ala Lys Glu Val Thr Arg Tyr Ser Val Ala Leu Ala Trp Leu Glu Pro
 450 455 460
 Asp Arg Pro Asn Gly Val Ile Leu Glu Tyr Glu Val Lys Tyr Tyr Glu
 465 470 475 480
 Lys Asp Gln Asn Glu Arg Ser Tyr Arg Ile Val Arg Thr Ala Ala Arg
 485 490 495
 Asn Thr Asp Ile Lys Gly Leu Asn Pro Leu Thr Ser Tyr Val Phe His
 500 505 510
 Val Arg Ala Arg Thr Ala Ala Gly Tyr Gly Asp Phe Ser Glu Pro Leu
 515 520 525
 Glu Val Thr Thr Asn Thr Val Pro Ser Arg Ile Ile Gly Asp Gly Ala
 530 535 540
 Asn Ser Thr Val Leu Leu Val Ser Val Ser Gly Ser Val Val Leu Val
 545 550 555 560
 Val Ile Leu Ile Ala Ala Phe Val Ile Ser Arg Arg Arg Ser Lys Tyr
 565 570 575
 Ser Lys Ala Lys Gln Glu Ala Asp Glu Glu Lys His Leu Asn Gln Gly
 580 585 590
 Val Arg Thr Tyr Val Asp Pro Phe Thr Tyr Glu Asp Pro Asn Gln Ala
 595 600 605
 Val Arg Glu Phe Ala Lys Glu Ile Asp Ala Ser Cys Ile Lys Ile Glu
 610 615 620
 Lys Val Ile Gly Val Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu
 625 630 635 640
 Lys Val Pro Gly Lys Arg Glu Ile Cys Val Ala Ile Lys Thr Leu Lys
 645 650 655
 Ala Gly Tyr Thr Asp Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser
 660 665 670
 Ile Met Gly Gln Phe Asp His Pro Asn Ile Ile His Leu Glu Gly Val
 675 680 685
 Val Thr Lys Cys Lys Pro Val Met Ile Ile Thr Glu Tyr Met Glu Asn
 690 695 700
 Gly Ser Leu Asp Ala Phe Leu Arg Lys Asn Asp Gly Arg Phe Thr Val
 705 710 715 720

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Ile Gln Leu Val Gly Met Leu Arg Gly Ile Gly Ser Gly Met Lys Tyr
 725 730 735
 Leu Ser Asp Met Ser Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile
 740 745 750
 Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Met Ser
 755 760 765
 Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly
 770 775 780
 Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ala Tyr Arg Lys
 785 790 795 800
 Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu
 805 810 815
 Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp
 820 825 830
 Val Ile Lys Ala Ile Glu Glu Gly Tyr Arg Leu Pro Pro Pro Met Asp
 835 840 845
 Cys Pro Ile Ala Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Glu
 850 855 860
 Arg Ser Asp Arg Pro Lys Phe Gly Gln Ile Val Asn Met Leu Asp Lys
 865 870 875 880
 Leu Ile Arg Asn Pro Asn Ser Leu Lys Arg Thr Gly Thr Glu Ser Ser
 885 890 895
 Arg Pro Asn Thr Ala Leu Leu Asp Pro Ser Ser Pro Glu Phe Ser Ala
 900 905 910
 Val Val Ser Val Gly Asp Trp Leu Gln Ala Ile Lys Met Asp Arg Tyr
 915 920 925
 Lys Asp Asn Phe Thr Ala Ala Gly Tyr Thr Thr Leu Glu Ala Val Val
 930 935 940
 His Val Asn Gln Glu Asp Leu Ala Arg Ile Gly Ile Thr Ala Ile Thr
 945 950 955 960
 His Gln Asn Lys Ile Leu Ser Ser Val Gln Ala Met Arg Thr Gln Met
 965 970 975
 Gln Gln Met His Gly Arg Met Val Pro Val
 980 985

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(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4529 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 186..3182

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CGGTGCGAGC GAACAGGAGT GGGGGGGAAA TTAAAAAAG CTAAACGTGG AGCAGCCGAT	60
CGGGGACCGA GAAGGGGAAT CGATGCAAGG AGCACACTAA AACAAAAGCT ACTTCGGAAC	120
AAACAGCATT TAAAAATCCA CGACTCAAGA TAACTGAAAC CTAAAATAAA ACCTGCTCAT	180
GCACC ATG GTT TTT CAA ACT CGG TAC CCT TCA TGG ATT ATT TTA TGC	227
Met Val Phe Gln Thr Arg Tyr Pro Ser Trp Ile Ile Leu Cys	
1 5 10	
TAC ATC TGG CTG CTC CGC TTT GCA CAC ACA GGG GAG GCG CAG GCT GCG	275
Tyr Ile Trp Leu Leu Arg Phe Ala His Thr Gly Glu Ala Gln Ala Ala	
15 20 25 30	
AAG GAA GTA CTA CTG CTG GAT TCT AAA GCA CAA CAA ACA GAG TTG GAG	323
Lys Glu Val Leu Leu Leu Asp Ser Lys Ala Gln Gln Thr Glu Leu Glu	
35 40 45	
TGG ATT TCC TCT CCA CCC AAT GGG TGG GAA GAA ATT AGT GGT TTG GAT	371
Trp Ile Ser Ser Pro Pro Asn Gly Trp Glu Glu Ile Ser Gly Leu Asp	
50 55 60	
GAG AAC TAT ACC CCG ATA CGA ACA TAC CAG GTG TGC CAA GTC ATG GAG	419
Glu Asn Tyr Thr Pro Ile Arg Thr Tyr Gln Val Cys Gln Val Met Glu	
65 70 75	
CCC AAC CAA AAC AAC TGG CTG CGG ACT AAC TGG ATT TCC AAA GGC AAT	467
Pro Asn Gln Asn Asn Trp Leu Arg Thr Asn Trp Ile Ser Lys Gly Asn	
80 85 90	
GCA CAA AGG ATT TTT GTA GAA TTG AAA TTC ACC CTG AGG GAT TGT AAC	515
Ala Gln Arg Ile Phe Val Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn	
95 100 105 110	
AGT CTT CCT GGA GTA CTG GGA ACT TGC AAG GAA ACA TTT AAT TTG TAC	563
Ser Leu Pro Gly Val Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr	
115 120 125	

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TAT TAT GAA ACA GAC TAT GAC ACT GGC AGG AAT ATA AGA GAA AAC CTC	611
Tyr Tyr Glu Thr Asp Tyr Asp Thr Gly Arg Asn Ile Arg Glu Asn Leu	
130 135 140	
TAT GTA AAA ATA GAC ACC ATT GCT GCA GAT GAA AGT TTT ACC CAA GGT	659
Tyr Val Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Gly	
145 150 155	
GAC CTT GGT GAA AGA AAG ATG AAG CTT AAC ACT GAG GTG AGA GAG ATT	707
Asp Leu Gly Glu Arg Lys Met Lys Leu Asn Thr Glu Val Arg Glu Ile	
160 165 170	
GGA CCT TTG TCC AAA AAG GGA TTC TAT CTT GCC TTT CAG GAT GTA GGG	755
Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly	
175 180 185 190	
GCT TGC ATA GCT TTG GTT TCT GTC AAA GTG TAC TAC AAG AAG TGC TGG	803
Ala Cys Ile Ala Leu Val Ser Val Lys Val Tyr Tyr Lys Lys Cys Trp	
195 200 205	
TCC ATT ATT GAG AAC TTA GCT ATC TTT CCA GAT ACA GTG ACT GGT TCA	851
Ser Ile Ile Glu Asn Leu Ala Ile Phe Pro Asp Thr Val Thr Gly Ser	
210 215 220	
GAA TTT TCC TCT TTA GTC GAG GTT CGA GGG ACA TGT GTC AGC AGT GCA	899
Glu Phe Ser Ser Leu Val Glu Val Arg Gly Thr Cys Val Ser Ser Ala	
225 230 235	
GAG GAA GAA GCG GAA AAC GCC CCC AGG ATG CAC TGC AGT GCA GAA GGA	947
Glu Glu Glu Ala Glu Asn Ala Pro Arg Met His Cys Ser Ala Glu Gly	
240 245 250	
GAA TGG TTA GTG CCC ATT GGA AAA TGT ATC TGC AAA GCA GGC TAC CAG	995
Glu Trp Leu Val Pro Ile Gly Lys Cys Ile Cys Lys Ala Gly Tyr Gln	
255 260 265 270	
CAA AAA GGA GAC ACT TGT GAA CCC TGT GGC CGT GGG TTC TAC AAG TCT	1043
Gln Lys Gly Asp Thr Cys Glu Pro Cys Gly Arg Gly Phe Tyr Lys Ser	
275 280 285	
TCC TCT CAA GAT CTT CAG TGC TCT CGT TGT CCA ACT CAC AGT TTT TCT	1091
Ser Ser Gln Asp Leu Gln Cys Ser Arg Cys Pro Thr His Ser Phe Ser	
290 295 300	
GAT AAA GAA GGC TCC TCC AGA TGT GAA TGT GAA GAT GGG TAT TAC AGG	1139
Asp Lys Glu Gly Ser Ser Arg Cys Glu Cys Glu Asp Gly Tyr Tyr Arg	
305 310 315	
GCT CCA TCT GAC CCA CCA TAC GTT GCA TGC ACA AGG CCT CCA TCT GCA	1187
Ala Pro Ser Asp Pro Pro Tyr Val Ala Cys Thr Arg Pro Pro Ser Ala	
320 325 330	
CCA CAG AAC CTC ATT TTC AAC ATC AAC CAA ACC ACA GTA AGT TTG GAA	1235
Pro Gln Asn Leu Ile Phe Asn Ile Asn Gln Thr Thr Val Ser Leu Glu	
335 340 345 350	

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TGG AGT CCT CCT GCA GAC AAT GGG GGA AGA AAC GAT GTG ACC TAC AGA	1283
Trp Ser Pro Pro Ala Asp Asn Gly Gly Arg Asn Asp Val Thr Tyr Arg	
355 360 365	
ATA TTG TGT AAG CGG TGC AGT TGG GAG CAG GGC GAA TGT GTT CCC TGT	1331
Ile Leu Cys Lys Arg Cys Ser Trp Glu Gln Gly Glu Cys Val Pro Cys	
370 375 380	
GGG AGT AAC ATT GGA TAC ATG CCC CAG CAG ACT GGA TTA GAG GAT AAC	1379
Gly Ser Asn Ile Gly Tyr Met Pro Gln Gln Thr Gly Leu Glu Asp Asn	
385 390 395	
TAT GTC ACT GTC ATG GAC CTG CTA GCC CAC GCT AAT TAT ACT TTT GAA	1427
Tyr Val Thr Val Met Asp Leu Leu Ala His Ala Asn Tyr Thr Phe Glu	
400 405 410	
GTT GAA GCT GTA AAT GGA GTT TCT GAC TTA AGC CGA TCC CAG AGG CTC	1475
Val Glu Ala Val Asn Gly Val Ser Asp Leu Ser Arg Ser Gln Arg Leu	
415 420 425 430	
TTT GCT GCT GTC AGT ATC ACC ACT GGT CAA GCA GCT CCC TCG CAA GTG	1523
Phe Ala Ala Val Ser Ile Thr Thr Gly Gln Ala Ala Pro Ser Gln Val	
435 440 445	
AGC GGA GTA ATG AAG GAG AGA GTA CTG CAG CGG AGT GTC GAG CTT TCC	1571
Ser Gly Val Met Lys Glu Arg Val Leu Gln Arg Ser Val Glu Leu Ser	
450 455 460	
TGG CAG GAA CCA GAG CAT CCC AAT GGA GTC ATC ACA GAA TAT GAA ATC	1619
Trp Gln Glu Pro Glu His Pro Asn Gly Val Ile Thr Glu Tyr Glu Ile	
465 470 475	
AAG TAT TAC GAG AAA GAT CAA AGG GAA CGG ACC TAC TCA ACA GTA AAA	1667
Lys Tyr Tyr Glu Lys Asp Gln Arg Glu Arg Thr Tyr Ser Thr Val Lys	
480 485 490	
ACC AAG TCT ACT TCA GCC TCC ATT AAT AAT CTG AAA CCA GGA ACA GTG	1715
Thr Lys Ser Thr Ser Ala Ser Ile Asn Asn Leu Lys Pro Gly Thr Val	
495 500 505 510	
TAT GTT TTC CAG ATT CGG GCT TTT ACT GCT GCT GGT TAT GGA AAT TAC	1763
Tyr Val Phe Gln Ile Arg Ala Phe Thr Ala Ala Gly Tyr Gly Asn Tyr	
515 520 525	
AGT CCC AGA CTT GAT GTT GCT ACA CTA GAG GAA GCT ACA GGT AAA ATG	1811
Ser Pro Arg Leu Asp Val Ala Thr Leu Glu Glu Ala Thr Gly Lys Met	
530 535 540	
TTT GAA GCT ACA GCT GTC TCC AGT GAA CAG AAT CCT GTT ATT ATC ATT	1859
Phe Glu Ala Thr Ala Val Ser Ser Glu Gln Asn Pro Val Ile Ile Ile	
545 550 555	
GCT GTG GTT GCT GTA GCT GGG ACC ATC ATT TTG GTG TTC ATG GTC TTT	1907
Ala Val Val Ala Val Ala Gly Thr Ile Ile Leu Val Phe Met Val Phe	
560 565 570	

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GGC	TTC	ATC	ATT	GGG	AGA	AGG	CAC	TGT	GGT	TAT	AGC	AAA	GCT	GAC	CAA	1955
Gly	Phe	Ile	Ile	Gly	Arg	Arg	His	Cys	Gly	Tyr	Ser	Lys	Ala	Asp	Gln	
575					580					585					590	
GAA	GGC	GAT	GAA	GAG	CTT	TAC	TTT	CAT	TTT	AAA	TTT	CCA	GGC	ACC	AAA	2003
Glu	Gly	Asp	Glu	Glu	Leu	Tyr	Phe	His	Phe	Lys	Phe	Pro	Gly	Thr	Lys	
				595					600					605		
ACC	TAC	ATT	GAC	CCT	GAA	ACC	TAT	GAG	GAC	CCA	AAT	AGA	GCT	GTC	CAT	2051
Thr	Tyr	Ile	Asp	Pro	Glu	Thr	Tyr	Glu	Asp	Pro	Asn	Arg	Ala	Val	His	
			610					615					620			
CAA	TTC	GCC	AAG	GAG	CTA	GAT	GCC	TCC	TGT	ATT	AAA	ATT	GAG	CGT	GTG	2099
Gln	Phe	Ala	Lys	Glu	Leu	Asp	Ala	Ser	Cys	Ile	Lys	Ile	Glu	Arg	Val	
		625					630						635			
ATT	GGT	GCA	GGA	GAA	TTC	GGT	GAA	GTC	TGC	AGT	GGC	CGT	TTG	AAA	CTT	2147
Ile	Gly	Ala	Gly	Glu	Phe	Gly	Glu	Val	Cys	Ser	Gly	Arg	Leu	Lys	Leu	
	640					645					650					
CCA	GGG	AAA	AGA	GAT	GTT	GCA	GTA	GCC	ATA	AAA	ACC	CTG	AAA	GTT	GGT	2195
Pro	Gly	Lys	Arg	Asp	Val	Ala	Val	Ala	Ile	Lys	Thr	Leu	Lys	Val	Gly	
655					660					665					670	
TAC	ACA	GAA	AAA	CAA	AGG	AGA	GAC	TTT	TTG	TGT	GAA	GCA	AGC	ATC	ATG	2243
Tyr	Thr	Glu	Lys	Gln	Arg	Arg	Asp	Phe	Leu	Cys	Glu	Ala	Ser	Ile	Met	
				675					680					685		
GGG	CAG	TTT	GAC	CAC	CCA	AAT	GTT	GTC	CAT	TTG	GAA	GGG	GTT	GTT	ACA	2291
Gly	Gln	Phe	Asp	His	Pro	Asn	Val	Val	His	Leu	Glu	Gly	Val	Val	Thr	
			690					695					700			
AGA	GGG	AAA	CCA	GTC	ATG	ATA	GTA	ATA	GAG	TTC	ATG	GAA	AAT	GGA	GCC	2339
Arg	Gly	Lys	Pro	Val	Met	Ile	Val	Ile	Glu	Phe	Met	Glu	Asn	Gly	Ala	
		705					710					715				
CTA	GAT	GCA	TTT	CTC	AGG	AAA	CAT	GAT	GGG	CAA	TTT	ACA	GTC	ATT	CAG	2387
Leu	Asp	Ala	Phe	Leu	Arg	Lys	His	Asp	Gly	Gln	Phe	Thr	Val	Ile	Gln	
	720					725					730					
TTA	GTA	GGA	ATG	CTG	AGA	GGA	ATT	GCT	GCT	GGA	ATG	AGA	TAT	TTG	GCT	2435
Leu	Val	Gly	Met	Leu	Arg	Gly	Ile	Ala	Ala	Gly	Met	Arg	Tyr	Leu	Ala	
735					740					745					750	
GAT	ATG	GGA	TAT	GTT	CAC	AGG	GAC	CTT	GCA	GCT	CGC	AAT	ATT	CTT	GTC	2483
Asp	Met	Gly	Tyr	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Val	
				755					760					765		
AAC	AGC	AAT	CTC	GTT	TGT	AAA	GTG	TCA	GAT	TTT	GGC	CTG	TCC	CGA	GTT	2531
Asn	Ser	Asn	Leu	Val	Cys	Lys	Val	Ser	Asp	Phe	Gly	Leu	Ser	Arg	Val	
			770					775					780			
ATA	GAG	GAT	GAT	CCA	GAA	GCT	GTC	TAT	ACA	ACT	ACT	GGT	GGA	AAA	ATT	2579
Ile	Glu	Asp	Asp	Pro	Glu	Ala	Val	Tyr	Thr	Thr	Thr	Gly	Gly	Lys	Ile	
		785					790					795				

CCA GTA AGG TGG ACA GCA CCC GAA GCC ATC CAG TAC CGG AAA TTC ACA Pro Val Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr Arg Lys Phe Thr 800 805 810	2627
TCA GCC AGT GAT GTA TGG AGC TAT GGA ATA GTC ATG TGG GAA GTT ATG Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met 815 820 825 830	2675
TCT TAT GGA GAA AGA CCT TAT TGG GAC ATG TCA AAT CAA GAT GTT ATA Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile 835 840 845	2723
AAA GCA ATA GAA GAA GGT TAT CGT TTA CCA GCA CCC ATG GAC TGC CCA Lys Ala Ile Glu Glu Gly Tyr Arg Leu Pro Ala Pro Met Asp Cys Pro 850 855 860	2771
GCT GGC CTT CAC CAG CTA ATG TTG GAT TGT TGG CAA AAG GAG CGT GCT Ala Gly Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Glu Arg Ala 865 870 875	2819
GAA AGG CCA AAA TTT GAA CAG ATA GTT GGA ATT CTA GAC AAA ATG ATT Glu Arg Pro Lys Phe Glu Gln Ile Val Gly Ile Leu Asp Lys Met Ile 880 885 890	2867
CGA AAC CCA AAT AGT CTG AAA ACT CCC CTG GGA ACT TGT AGT AGG CCA Arg Asn Pro Asn Ser Leu Lys Thr Pro Leu Gly Thr Cys Ser Arg Pro 895 900 905 910	2915
ATA AGC CCT CTT CTG GAT CAA AAC ACT CCT GAT TTC ACT ACC TTT TGT Ile Ser Pro Leu Leu Asp Gln Asn Thr Pro Asp Phe Thr Thr Phe Cys 915 920 925	2963
TCA GTT GGA GAA TGG CTA CAA GCT ATT AAG ATG GAA AGA TAT AAA GAT Ser Val Gly Glu Trp Leu Gln Ala Ile Lys Met Glu Arg Tyr Lys Asp 930 935 940	3011
AAT TTC ACG GCA GCT GGC TAC AAT TCC CTT GAA TCA GTA GCC AGG ATG Asn Phe Thr Ala Ala Gly Tyr Asn Ser Leu Glu Ser Val Ala Arg Met 945 950 955	3059
ACT ATT GAG GAT GTG ATG AGT TTA GGG ATC ACA CTG GTT GGT CAT CAA Thr Ile Glu Asp Val Met Ser Leu Gly Ile Thr Leu Val Gly His Gln 960 965 970	3107
AAG AAA ATC ATG AGC AGC ATT CAG ACT ATG AGA GCA CAA ATG CTA CAT Lys Lys Ile Met Ser Ser Ile Gln Thr Met Arg Ala Gln Met Leu His 975 980 985 990	3155
TTA CAT GGA ACT GGC ATT CAA GTG TGATATGCAT TTCTCCCTTT TAAGGGAGAT Leu His Gly Thr Gly Ile Gln Val 995	3209
TACAGACTGC AAGAGAACAG TACTGGCCTT CAGTATATGC ATAGAATGCT GCTAGAAGAC	3269
AAGTGATGTC CTGGGTCCTT CCAACAGTGA AGAGAAGATT TAAGAAGCAC CTATAGACTT	3329
GAACCTCCTAA GTGCCACCAG AATATATAAA AAGGGAATTT AGGATCCACC ATCGGTGGCC	3389

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AGGAAAATAG CAGTGACAAT AAACAAAGTA CTACCTGAAA AACATCCAAA CACCTTGAGC 3449
 TCTCTAACCT CCTTTTTGTC TTATAGACTT TTTAAAATGT ACATAAGAA TTTAAGAAAG 3509
 AATATATTTG TCAAATAAAA TCATGATCTT ATTGTAAAA TTAATGAAAT ATTTTCCTTA 3569
 AATATGTGAT TTCAGACTAT TCCTTTTTTA AATCATTGT GTTTATTCTT CATAAGGACT 3629
 TTGTTTTAGA AAGCTGTTTA TAGCTTTGGA CCTTTTTAGT GTTAAATCTG TAACATTACT 3689
 ACAC TGGGTA CCTTTGAAAG AATCTCAAT TTCAAAGAA ATAGCATGAT TGAAGATACA 3749
 TCTCTGTTAG AACATTGGTA TCCTTTTTGT GCCATTTTAT TCTGTTTAAT CAGTGCTGTT 3809
 TTGATATTGT TTGCTAATTG GCAGGTAGTC AAGAAAATGC AAGTTGCCAA GAGCTCTGAT 3869
 ATTTTTTAAA AAGAATTTTT TTGTAAAGAT CAGACAACAC ACTATCTTTT CAATGAAAAA 3929
 AGCAATAATG ATCCATACAT ACTATAAGGC ACTTTTAACA GATTGTTTAT AGAGTGATTT 3989
 TACTAGAAAG AATTTAATAA ACTCGAAGTT TAGGTTTATG AGTATATAAA CAAATGAGGC 4049
 ACTTCATCTG AAGAATGTTG GTGAAGGCAA GTCTCTGAAA GCAGAACTAT CCAGTGTTAT 4109
 CTA AAAATTA ATCTGAGCAC ATCAAGATTT TTTCATTCTC GTGACATTAG GAAATTTAGG 4169
 ATAAATAGTT GACATATATT TTATATCCTC TTCTGTTGAA TGCAGTCCAA ACATGAAAGG 4229
 AAATAATTGT TTTATATTAT AACTCTGAAG CATGATAAAG GGGCAGTTCA CAATTTTCAC 4289
 CATTTAAACA CAAATTTGCT GCACAGAATA TCACCATTGC AGTTCAAAC AAAACAAAAC 4349
 AAAAAGTCTT TTGTTTGTGA AACTGATGC AAGAACTTG TTAAATGAAA GGA CTCTTTA 4409
 CCCTAGAAGG AAGAGGTGAA GGATCTGGCT TGTTTTTAAA GCTTTATTTA TTAAACCATA 4469
 TTATTTGATT ACTGTGTTAG AATTCATAA GCAATAATTA AATGTGTCTT TATGGAATTC 4529

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 998 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Met Val Phe Gln Thr Arg Tyr Pro Ser Trp Ile Ile Leu Cys Tyr Ile
 1 5 10 15
 Trp Leu Leu Arg Phe Ala His Thr Gly Glu Ala Gln Ala Ala Lys Glu
 20 25 30

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Val Leu Leu Leu Asp Ser Lys Ala Gln Gln Thr Glu Leu Glu Trp Ile
 35 40 45
 Ser Ser Pro Pro Asn Gly Trp Glu Glu Ile Ser Gly Leu Asp Glu Asn
 50 55 60
 Tyr Thr Pro Ile Arg Thr Tyr Gln Val Cys Gln Val Met Glu Pro Asn
 65 70 75 80
 Gln Asn Asn Trp Leu Arg Thr Asn Trp Ile Ser Lys Gly Asn Ala Gln
 85 90 95
 Arg Ile Phe Val Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn Ser Leu
 100 105 110
 Pro Gly Val Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Tyr
 115 120 125
 Glu Thr Asp Tyr Asp Thr Gly Arg Asn Ile Arg Glu Asn Leu Tyr Val
 130 135 140
 Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Gly Asp Leu
 145 150 155 160
 Gly Glu Arg Lys Met Lys Leu Asn Thr Glu Val Arg Glu Ile Gly Pro
 165 170 175
 Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys
 180 185 190
 Ile Ala Leu Val Ser Val Lys Val Tyr Tyr Lys Lys Cys Trp Ser Ile
 195 200 205
 Ile Glu Asn Leu Ala Ile Phe Pro Asp Thr Val Thr Gly Ser Glu Phe
 210 215 220
 Ser Ser Leu Val Glu Val Arg Gly Thr Cys Val Ser Ser Ala Glu Glu
 225 230 235 240
 Glu Ala Glu Asn Ala Pro Arg Met His Cys Ser Ala Glu Gly Glu Trp
 245 250 255
 Leu Val Pro Ile Gly Lys Cys Ile Cys Lys Ala Gly Tyr Gln Gln Lys
 260 265 270
 Gly Asp Thr Cys Glu Pro Cys Gly Arg Gly Phe Tyr Lys Ser Ser Ser
 275 280 285
 Gln Asp Leu Gln Cys Ser Arg Cys Pro Thr His Ser Phe Ser Asp Lys
 290 295 300
 Glu Gly Ser Ser Arg Cys Glu Cys Glu Asp Gly Tyr Tyr Arg Ala Pro
 305 310 315 320
 Ser Asp Pro Pro Tyr Val Ala Cys Thr Arg Pro Pro Ser Ala Pro Gln
 325 330 335

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Asn Leu Ile Phe Asn Ile Asn Gln Thr Thr Val Ser Leu Glu Trp Ser
 340 345 350
 Pro Pro Ala Asp Asn Gly Gly Arg Asn Asp Val Thr Tyr Arg Ile Leu
 355 360 365
 Cys Lys Arg Cys Ser Trp Glu Gln Gly Glu Cys Val Pro Cys Gly Ser
 370 375 380
 Asn Ile Gly Tyr Met Pro Gln Gln Thr Gly Leu Glu Asp Asn Tyr Val
 385 390 395 400
 Thr Val Met Asp Leu Leu Ala His Ala Asn Tyr Thr Phe Glu Val Glu
 405 410 415
 Ala Val Asn Gly Val Ser Asp Leu Ser Arg Ser Gln Arg Leu Phe Ala
 420 425 430
 Ala Val Ser Ile Thr Thr Gly Gln Ala Ala Pro Ser Gln Val Ser Gly
 435 440 445
 Val Met Lys Glu Arg Val Leu Gln Arg Ser Val Glu Leu Ser Trp Gln
 450 455 460
 Glu Pro Glu His Pro Asn Gly Val Ile Thr Glu Tyr Glu Ile Lys Tyr
 465 470 475 480
 Tyr Glu Lys Asp Gln Arg Glu Arg Thr Tyr Ser Thr Val Lys Thr Lys
 485 490 495
 Ser Thr Ser Ala Ser Ile Asn Asn Leu Lys Pro Gly Thr Val Tyr Val
 500 505 510
 Phe Gln Ile Arg Ala Phe Thr Ala Ala Gly Tyr Gly Asn Tyr Ser Pro
 515 520 525
 Arg Leu Asp Val Ala Thr Leu Glu Glu Ala Thr Gly Lys Met Phe Glu
 530 535 540
 Ala Thr Ala Val Ser Ser Glu Gln Asn Pro Val Ile Ile Ile Ala Val
 545 550 555 560
 Val Ala Val Ala Gly Thr Ile Ile Leu Val Phe Met Val Phe Gly Phe
 565 570 575
 Ile Ile Gly Arg Arg His Cys Gly Tyr Ser Lys Ala Asp Gln Glu Gly
 580 585 590
 Asp Glu Glu Leu Tyr Phe His Phe Lys Phe Pro Gly Thr Lys Thr Tyr
 595 600 605
 Ile Asp Pro Glu Thr Tyr Glu Asp Pro Asn Arg Ala Val His Gln Phe
 610 615 620
 Ala Lys Glu Leu Asp Ala Ser Cys Ile Lys Ile Glu Arg Val Ile Gly
 625 630 635 640

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Ala Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Leu Pro Gly
 645 650 655
 Lys Arg Asp Val Ala Val Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr
 660 665 670
 Glu Lys Gln Arg Arg Asp Phe Leu Cys Glu Ala Ser Ile Met Gly Gln
 675 680 685
 Phe Asp His Pro Asn Val Val His Leu Glu Gly Val Val Thr Arg Gly
 690 695 700
 Lys Pro Val Met Ile Val Ile Glu Phe Met Glu Asn Gly Ala Leu Asp
 705 710 715 720
 Ala Phe Leu Arg Lys His Asp Gly Gln Phe Thr Val Ile Gln Leu Val
 725 730 735
 Gly Met Leu Arg Gly Ile Ala Ala Gly Met Arg Tyr Leu Ala Asp Met
 740 745 750
 Gly Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser
 755 760 765
 Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val Ile Glu
 770 775 780
 Asp Asp Pro Glu Ala Val Tyr Thr Thr Thr Gly Gly Lys Ile Pro Val
 785 790 795 800
 Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr Arg Lys Phe Thr Ser Ala
 805 810 815
 Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met Ser Tyr
 820 825 830
 Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile Lys Ala
 835 840 845
 Ile Glu Glu Gly Tyr Arg Leu Pro Ala Pro Met Asp Cys Pro Ala Gly
 850 855 860
 Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Glu Arg Ala Glu Arg
 865 870 875 880
 Pro Lys Phe Glu Gln Ile Val Gly Ile Leu Asp Lys Met Ile Arg Asn
 885 890 895
 Pro Asn Ser Leu Lys Thr Pro Leu Gly Thr Cys Ser Arg Pro Ile Ser
 900 905 910
 Pro Leu Leu Asp Gln Asn Thr Pro Asp Phe Thr Thr Phe Cys Ser Val
 915 920 925
 Gly Glu Trp Leu Gln Ala Ile Lys Met Glu Arg Tyr Lys Asp Asn Phe
 930 935 940

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Thr Ala Ala Gly Tyr Asn Ser Leu Glu Ser Val Ala Arg Met Thr Ile
 945 950 955 960

Glu Asp Val Met Ser Leu Gly Ile Thr Leu Val Gly His Gln Lys Lys
 965 970 975

Ile Met Ser Ser Ile Gln Thr Met Arg Ala Gln Met Leu His Leu His
 980 985 990

Gly Thr Gly Ile Gln Val
 995

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 976 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Glu Leu Gln Ala Ala Arg Ala Cys Phe Ala Leu Leu Trp Gly Cys
 1 5 10 15

Ala Leu Ala Ala Ala Ala Ala Gln Gly Lys Glu Val Val Leu Leu
 20 25 30

Asp Phe Ala Ala Ala Gly Gly Glu Leu Gly Trp Leu Thr His Pro Tyr
 35 40 45

Gly Lys Gly Trp Asp Leu Met Gln Asn Ile Met Asn Asp Met Pro Ile
 50 55 60

Tyr Met Tyr Ser Val Cys Asn Val Met Ser Gly Asp Gln Asp Asn Trp
 65 70 75 80

Leu Arg Thr Asn Trp Val Tyr Arg Gly Glu Ala Glu Arg Asn Asn Phe
 85 90 95

Glu Leu Asn Phe Thr Val Arg Asp Cys Asn Ser Phe Pro Gly Gly Ala
 100 105 110

Ser Ser Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Ala Glu Ser Asp Leu
 115 120 125

Asp Tyr Gly Thr Asn Phe Gln Lys Arg Leu Phe Thr Lys Ile Asp Thr
 130 135 140

Ile Ala Pro Asp Glu Ile Thr Val Ser Ser Asp Phe Glu Ala Arg His
 145 150 155 160

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Val Lys Leu Asn Val Glu Glu Arg Ser Val Gly Pro Leu Thr Arg Lys
 165 170 175
 Gly Phe Tyr Leu Ala Phe Gln Asp Ile Gly Ala Cys Val Ala Leu Leu
 180 185 190
 Ser Val Arg Val Tyr Tyr Lys Lys Cys Pro Glu Leu Leu Gln Gly Leu
 195 200 205
 Ala His Phe Pro Glu Thr Ile Ala Gly Ser Asp Ala Pro Ser Leu Ala
 210 215 220
 Thr Val Ala Gly Thr Cys Val Asp His Ala Val Val Pro Pro Gly Gly
 225 230 235 240
 Glu Glu Pro Arg Met His Cys Ala Val Asp Gly Glu Trp Leu Val Pro
 245 250 255
 Ile Gly Gln Cys Leu Cys Gln Ala Gly Tyr Glu Lys Val Glu Asp Ala
 260 265 270
 Cys Gln Ala Cys Ser Pro Gly Phe Phe Lys Phe Glu Ala Ser Glu Ser
 275 280 285
 Pro Cys Leu Glu Cys Pro Glu His Thr Leu Pro Ser Pro Glu Gly Ala
 290 295 300
 Thr Ser Cys Glu Cys Glu Glu Gly Phe Phe Arg Ala Pro Gln Asp Pro
 305 310 315 320
 Ala Ser Met Pro Cys Thr Arg Pro Pro Ser Ala Pro His Tyr Leu Thr
 325 330 335
 Ala Val Gly Met Gly Ala Lys Val Glu Leu Arg Trp Thr Pro Pro Gln
 340 345 350
 Asp Ser Gly Gly Arg Glu Asp Ile Val Tyr Ser Val Thr Cys Glu Gln
 355 360 365
 Cys Trp Pro Glu Ser Gly Glu Cys Gly Pro Cys Glu Ala Ser Val Arg
 370 375 380
 Tyr Ser Glu Pro Pro His Gly Leu Thr Arg Thr Ser Val Thr Val Ser
 385 390 395 400
 Asp Leu Glu Pro His Met Asn Tyr Thr Phe Thr Val Glu Ala Arg Asn
 405 410 415
 Gly Val Ser Gly Leu Val Thr Ser Arg Ser Phe Arg Thr Ala Ser Val
 420 425 430
 Ser Ile Asn Gln Thr Glu Pro Pro Lys Val Arg Leu Glu Gly Arg Ser
 435 440 445
 Thr Thr Ser Leu Ser Val Ser Trp Ser Ile Pro Pro Pro Gln Gln Ser
 450 455 460

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Arg Val Trp Lys Tyr Glu Val Thr Tyr Arg Lys Lys Gly Asp Ser Asn
 465 470 475 480
 Ser Tyr Asn Val Arg Arg Thr Glu Gly Phe Ser Val Thr Leu Asp Asp
 485 490 495
 Leu Ala Pro Asp Thr Thr Tyr Leu Val Gln Val Gln Ala Leu Thr Gln
 500 505 510
 Glu Gly Gln Gly Ala Gly Ser Lys Val His Glu Phe Gln Thr Leu Ser
 515 520 525
 Pro Glu Gly Ser Gly Asn Leu Ala Val Ile Gly Gly Val Ala Val Gly
 530 535 540
 Val Val Leu Leu Leu Val Leu Ala Gly Val Gly Phe Phe Ile His Arg
 545 550 555 560
 Arg Arg Lys Asn Gln Arg Ala Arg Gln Ser Pro Glu Asp Val Tyr Phe
 565 570 575
 Ser Lys Ser Glu Gln Leu Lys Pro Leu Lys Thr Tyr Val Asp Pro His
 580 585 590
 Thr Tyr Glu Asp Pro Asn Gln Ala Val Leu Lys Phe Thr Thr Glu Ile
 595 600 605
 His Pro Ser Cys Val Thr Arg Gln Lys Val Ile Gly Ala Gly Glu Phe
 610 615 620
 Gly Glu Val Tyr Lys Gly Met Leu Lys Thr Ser Ser Gly Lys Lys Glu
 625 630 635 640
 Val Pro Val Ala Ile Lys Thr Leu Lys Ala Gly Tyr Thr Glu Lys Gln
 645 650 655
 Arg Val Asp Phe Leu Gly Glu Ala Gly Ile Met Gly Gln Phe Ser His
 660 665 670
 His Asn Ile Ile Arg Leu Glu Gly Val Ile Ser Lys Tyr Lys Pro Met
 675 680 685
 Met Ile Ile Thr Glu Tyr Met Glu Asn Gly Ala Leu Asp Lys Phe Leu
 690 695 700
 Arg Glu Lys Asp Gly Glu Phe Ser Val Leu Gln Leu Val Gly Met Leu
 705 710 715 720
 Arg Gly Ile Ala Ala Gly Met Lys Tyr Leu Ala Asn Met Asn Tyr Val
 725 730 735
 His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val
 740 745 750
 Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val Leu Glu Asp Asp Pro
 755 760 765

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Glu Ala Thr Tyr Thr Thr Ser Gly Gly Lys Ile Pro Ile Arg Trp Thr
 770 775 780
 Ala Pro Glu Ala Ile Ser Tyr Arg Lys Phe Thr Ser Ala Ser Asp Val
 785 790 795 800
 Trp Ser Phe Gly Ile Val Met Trp Glu Val Met Thr Tyr Gly Glu Arg
 805 810 815
 Pro Tyr Trp Glu Leu Ser Asn His Glu Val Met Lys Ala Ile Asn Asp
 820 825 830
 Gly Phe Arg Leu Pro Thr Pro Met Asp Cys Pro Ser Ala Ile Tyr Gln
 835 840 845
 Leu Met Met Gln Cys Trp Gln Gln Glu Arg Ala Arg Arg Pro Lys Phe
 850 855 860
 Ala Asp Ile Val Ser Ile Leu Asp Lys Leu Ile Arg Ala Pro Asp Ser
 865 870 875 880
 Leu Lys Thr Leu Ala Asp Phe Asp Pro Arg Val Ser Ile Arg Leu Pro
 885 890 895
 Ser Thr Ser Gly Ser Glu Gly Val Pro Phe Arg Thr Val Ser Glu Trp
 900 905 910
 Leu Glu Ser Ile Lys Met Gln Gln Tyr Thr Glu His Phe Met Ala Ala
 915 920 925
 Gly Tyr Thr Ala Ile Glu Lys Val Val Gln Met Thr Asn Asp Asp Ile
 930 935 940
 Lys Arg Ile Gly Val Arg Leu Pro Gly His Gln Lys Arg Ile Ala Tyr
 945 950 955 960
 Ser Leu Leu Gly Leu Lys Asp Gln Val Asn Thr Val Gly Ile Pro Ile
 965 970 975

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 984 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Met Glu Arg Arg Trp Pro Leu Gly Leu Gly Leu Val Leu Leu Cys
 1 5 10 15

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Ala Pro Leu Pro Pro Gly Ala Arg Ala Lys Glu Val Thr Leu Met Asp
 20 25 30
 Thr Ser Lys Ala Gln Gly Glu Leu Gly Trp Leu Leu Asp Pro Pro Lys
 35 40 45
 Asp Gly Trp Ser Glu Gln Gln Gln Ile Leu Asn Gly Thr Pro Leu Tyr
 50 55 60
 Met Tyr Gln Asp Cys Pro Met Gln Gly Arg Arg Asp Thr Asp His Trp
 65 70 75 80
 Leu Arg Ser Asn Trp Ile Tyr Arg Gly Glu Glu Ala Ser Arg Val His
 85 90 95
 Val Glu Leu Gln Phe Thr Val Arg Asp Cys Lys Ser Phe Pro Gly Gly
 100 105 110
 Ala Gly Pro Leu Gly Cys Lys Glu Thr Phe Asn Leu Leu Tyr Met Glu
 115 120 125
 Ser Asp Gln Asp Val Gly Ile Gln Leu Arg Arg Pro Leu Phe Gln Lys
 130 135 140
 Val Thr Thr Val Ala Ala Asp Gln Ser Phe Thr Ile Arg Asp Leu Ala
 145 150 155 160
 Ser Gly Ser Val Lys Leu Asn Val Glu Arg Cys Ser Leu Gly Arg Leu
 165 170 175
 Thr Arg Arg Gly Leu Tyr Leu Ala Phe His Asn Pro Gly Ala Cys Val
 180 185 190
 Ala Leu Val Ser Val Arg Val Phe Tyr Gln Arg Cys Pro Glu Thr Leu
 195 200 205
 Asn Gly Leu Ala Gln Phe Pro Asp Thr Leu Pro Gly Pro Ala Gly Leu
 210 215 220
 Val Glu Val Ala Gly Thr Cys Leu Pro His Ala Arg Ala Ser Pro Arg
 225 230 235 240
 Pro Ser Gly Ala Pro Arg Met His Cys Ser Pro Asp Gly Glu Trp Leu
 245 250 255
 Val Pro Val Gly Arg Cys His Cys Glu Pro Gly Tyr Glu Glu Gly Gly
 260 265 270
 Ser Gly Glu Ala Cys Val Ala Cys Pro Ser Gly Ser Tyr Arg Met Asp
 275 280 285
 Met Asp Thr Pro His Cys Leu Thr Cys Pro Gln Gln Ser Thr Ala Glu
 290 295 300
 Ser Glu Gly Ala Thr Ile Cys Thr Cys Glu Ser Gly His Tyr Arg Ala
 305 310 315 320

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Pro Gly Glu Gly Pro Gln Val Ala Cys Thr Gly Pro Pro Ser Ala Pro
 325 330 335
 Arg Asn Leu Ser Phe Ser Ala Ser Gly Thr Gln Leu Ser Leu Arg Trp
 340 345 350
 Glu Pro Pro Ala Asp Thr Gly Gly Arg Gln Asp Val Arg Tyr Ser Val
 355 360 365
 Arg Cys Ser Gln Cys Gln Gly Thr Ala Gln Asp Gly Gly Pro Cys Gln
 370 375 380
 Pro Cys Gly Val Gly Val His Phe Ser Pro Gly Ala Arg Ala Leu Thr
 385 390 395 400
 Thr Pro Ala Val His Val Asn Gly Leu Glu Pro Tyr Ala Asn Tyr Thr
 405 410 415
 Phe Asn Val Glu Ala Gln Asn Gly Val Ser Gly Leu Gly Ser Ser Gly
 420 425 430
 His Ala Ser Thr Ser Val Ser Ile Ser Met Gly His Ala Glu Ser Leu
 435 440 445
 Ser Gly Leu Ser Leu Arg Leu Val Lys Lys Glu Pro Arg Gln Leu Glu
 450 455 460
 Leu Thr Trp Ala Gly Ser Arg Pro Arg Ser Pro Gly Ala Asn Leu Thr
 465 470 475 480
 Tyr Glu Leu His Val Leu Asn Gln Asp Glu Glu Arg Tyr Gln Met Val
 485 490 495
 Leu Glu Pro Arg Val Leu Leu Thr Glu Leu Gln Pro Asp Thr Tyr Tyr
 500 505 510
 Ile Val Arg Val Arg Met Leu Thr Pro Leu Gly Pro Gly Pro Phe Ser
 515 520 525
 Pro Asp His Glu Phe Arg Thr Ser Pro Pro Val Ser Arg Gly Leu Thr
 530 535 540
 Gly Gly Glu Ile Val Ala Val Ile Phe Gly Leu Leu Leu Gly Ala Ala
 545 550 555 560
 Leu Leu Leu Gly Ile Leu Val Phe Arg Ser Arg Arg Ala Gln Arg Gln
 565 570 575
 Arg Gln Gln Arg His Val Thr Ala Pro Pro Met Trp Ile Glu Arg Thr
 580 585 590
 Ser Cys Ala Glu Ala Leu Cys Gly Thr Ser Arg His Thr Arg Thr Leu
 595 600 605
 His Arg Glu Pro Trp Thr Leu Pro Gly Gly Trp Ser Asn Phe Pro Ser
 610 615 620

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Arg Glu Leu Asp Pro Ala Trp Leu Met Val Asp Thr Val Ile Gly Glu
 625 630 635 640
 Gly Glu Phe Gly Glu Val Tyr Arg Gly Thr Leu Arg Leu Pro Ser Gln
 645 650 655
 Asp Cys Lys Thr Val Ala Ile Lys Thr Leu Lys Asp Thr Ser Pro Gly
 660 665 670
 Gly Gln Trp Trp Asn Phe Leu Arg Glu Ala Thr Ile Met Gly Gln Phe
 675 680 685
 Ser His Pro His Ile Leu His Leu Glu Gly Val Val Thr Lys Arg Lys
 690 695 700
 Pro Ile Met Ile Ile Thr Glu Phe Met Glu Asn Ala Ala Leu Asp Ala
 705 710 715 720
 Phe Leu Arg Glu Arg Glu Asp Gln Leu Val Pro Gly Gln Leu Val Ala
 725 730 735
 Met Leu Gln Gly Ile Ala Ser Gly Met Asn Tyr Leu Ser Asn His Asn
 740 745 750
 Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Gln Asn
 755 760 765
 Leu Cys Cys Lys Val Ser Asp Phe Gly Leu Thr Arg Leu Leu Asp Asp
 770 775 780
 Phe Asp Gly Thr Tyr Glu Thr Gln Gly Gly Lys Ile Pro Ile Arg Trp
 785 790 795 800
 Thr Ala Pro Glu Ala Ile Ala His Arg Ile Phe Thr Thr Ala Ser Asp
 805 810 815
 Val Trp Ser Phe Gly Ile Val Met Trp Glu Val Leu Ser Phe Gly Asp
 820 825 830
 Lys Pro Tyr Gly Glu Met Ser Asn Gln Glu Val Met Lys Ser Ile Glu
 835 840 845
 Asp Gly Tyr Arg Leu Pro Pro Pro Val Asp Cys Pro Ala Pro Leu Tyr
 850 855 860
 Glu Leu Met Lys Asn Cys Trp Ala Tyr Asp Arg Ala Arg Arg Pro His
 865 870 875 880
 Phe Gln Lys Leu Gln Ala His Leu Glu Gln Leu Leu Ala Asn Pro His
 885 890 895
 Ser Leu Arg Thr Ile Ala Asn Phe Asp Pro Arg Val Thr Leu Arg Leu
 900 905 910
 Pro Ser Leu Ser Gly Ser Asp Gly Ile Pro Tyr Arg Thr Val Ser Glu
 915 920 925

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Trp Leu Glu Ser Ile Arg Met Lys Arg Tyr Ile Leu His Phe His Ser
 930 935 940

Ala Gly Leu Asp Thr Met Glu Cys Val Leu Glu Leu Thr Ala Glu Asp
 945 950 955 960

Leu Thr Gln Met Gly Ile Thr Leu Pro Gly His Gln Lys Arg Ile Leu
 965 970 975

Cys Ser Ile Gln Gly Phe Lys Asp
 980

(2) INFORMATION FOR SEQ ID NO:20:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 998 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met Ala Arg Ala Arg Pro Pro Pro Pro Ser Pro Pro Pro Gly Leu
 1 5 10 15
 Leu Pro Leu Leu Pro Pro Leu Leu Leu Leu Pro Leu Leu Leu Leu Pro
 20 25 30
 Ala Gly Cys Arg Ala Leu Glu Glu Thr Leu Met Asp Thr Lys Trp Val
 35 40 45
 Thr Ser Glu Leu Ala Trp Thr Ser His Pro Glu Ser Gly Trp Glu Glu
 50 55 60
 Val Ser Gly Tyr Asp Glu Ala Met Asn Pro Ile Arg Thr Tyr Gln Val
 65 70 75 80
 Cys Asn Val Arg Glu Ser Ser Gln Asn Asn Trp Leu Arg Thr Gly Phe
 85 90 95
 Ile Trp Arg Arg Asp Val Gln Arg Val Tyr Val Glu Leu Lys Phe Thr
 100 105 110
 Val Arg Asp Cys Asn Ser Ile Pro Asn Ile Pro Gly Ser Cys Lys Glu
 115 120 125
 Thr Phe Asn Leu Phe Tyr Tyr Glu Ala Asp Ser Asp Val Ala Ser Ala
 130 135 140
 Ser Ser Pro Phe Trp Met Glu Asn Pro Tyr Val Lys Val Asp Thr Ile
 145 150 155 160
 Ala Pro Asp Glu Ser Phe Ser Arg Leu Asp Ala Gly Arg Val Asn Thr
 165 170 175

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Lys Val Arg Ser Phe Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu Ala
 180 185 190
 Phe Gln Asp Gln Gly Ala Cys Met Ser Leu Ile Ser Val Arg Ala Phe
 195 200 205
 Tyr Lys Lys Cys Ala Ser Thr Thr Ala Gly Phe Ala Leu Phe Pro Glu
 210 215 220
 Thr Leu Thr Gly Ala Glu Pro Thr Ser Leu Val Ile Ala Pro Gly Thr
 225 230 235 240
 Cys Ile Pro Asn Ala Val Glu Val Ser Val Pro Leu Lys Leu Tyr Cys
 245 250 255
 Asn Gly Asp Gly Glu Trp Met Val Pro Val Gly Ala Cys Thr Cys Ala
 260 265 270
 Thr Gly His Glu Pro Ala Ala Lys Glu Ser Gln Cys Arg Pro Cys Pro
 275 280 285
 Pro Gly Ser Tyr Lys Ala Lys Gln Gly Glu Gly Pro Cys Leu Pro Cys
 290 295 300
 Pro Pro Asn Ser Arg Thr Thr Ser Pro Ala Ala Ser Ile Cys Thr Cys
 305 310 315 320
 His Asn Asn Phe Tyr Arg Ala Asp Ser Asp Ser Ala Asp Ser Ala Cys
 325 330 335
 Thr Thr Val Pro Ser Pro Pro Arg Gly Val Ile Ser Asn Val Asn Glu
 340 345 350
 Thr Ser Leu Ile Leu Glu Trp Ser Glu Pro Arg Asp Leu Gly Val Arg
 355 360 365
 Asp Asp Leu Leu Tyr Asn Val Ile Cys Lys Lys Cys His Gly Ala Gly
 370 375 380
 Gly Ala Ser Ala Cys Ser Arg Cys Asp Asp Asn Val Glu Phe Val Pro
 385 390 395 400
 Arg Gln Leu Gly Leu Ser Glu Pro Arg Val His Thr Ser His Leu Leu
 405 410 415
 Ala His Thr Arg Tyr Thr Phe Glu Val Gln Ala Val Asn Gly Val Ser
 420 425 430
 Gly Lys Ser Pro Leu Pro Pro Arg Tyr Ala Ala Val Asn Ile Thr Thr
 435 440 445
 Asn Gln Ala Ala Pro Ser Glu Val Pro Thr Leu Arg Leu His Ser Ser
 450 455 460
 Ser Gly Ser Ser Leu Thr Leu Ser Trp Ala Pro Pro Glu Arg Pro Asn
 465 470 475 480

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Asp Asp Pro Ser Asp Pro Thr Tyr Thr Ser Ser Leu Gly Gly Lys Ile
785                               795                               800

Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ala Tyr Arg Lys Phe Thr
                               805                               810                               815

Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met
                               820                               825                               830

Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile
                               835                               840                               845

Asn Ala Val Glu Gln Asp Tyr Arg Leu Pro Pro Pro Met Asp Cys Pro
                               850                               855                               860

Thr Ala Leu His Gln Leu Met Leu Asp Cys Trp Val Arg Asp Arg Asn
865                               870                               875                               880

Leu Arg Pro Lys Phe Ser Gln Ile Val Asn Thr Leu Asp Lys Leu Ile
                               885                               890                               895

Arg Asn Ala Ala Ser Leu Lys Val Ile Ala Ser Ala Gln Ser Gly Met
                               900                               905                               910

Ser Gln Pro Leu Leu Asp Arg Thr Val Pro Asp Tyr Thr Thr Phe Thr
                               915                               920                               925

Thr Val Gly Asp Trp Leu Asp Ala Ile Lys Met Gly Arg Tyr Lys Glu
930                               935                               940

Ser Phe Val Ser Ala Gly Phe Ala Ser Phe Asp Leu Val Ala Gln Met
945                               950                               955                               960

Thr Ala Glu Asp Leu Leu Arg Ile Gly Val Thr Leu Ala Gly His Gln
                               965                               970                               975

Lys Lys Ile Leu Ser Ser Ile Gln Asp Met Arg Leu Gln Met Asn Gln
980                               985                               990

Thr Leu Pro Val Gln Val
995

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(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 983 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

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Met Asp Cys Gln Leu Ser Ile Leu Leu Leu Leu Ser Cys Ser Val Leu
1                               5                               10                               15

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Asp Ser Phe Gly Glu Leu Ile Pro Gln Pro Ser Asn Glu Val Asn Leu
 20 25 30
 Leu Asp Ser Lys Thr Ile Gln Gly Glu Leu Gly Trp Ile Ser Tyr Pro
 35 40 45
 Ser His Gly Trp Glu Glu Ile Ser Gly Val Asp Glu His Tyr Thr Pro
 50 55 60
 Ile Arg Thr Tyr Gln Val Cys Asn Val Met Asp His Ser Gln Asn Asn
 65 70 75 80
 Trp Leu Arg Thr Asn Trp Val Pro Arg Asn Ser Ala Gln Lys Ile Tyr
 85 90 95
 Val Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn Ser Ile Pro Leu Val
 100 105 110
 Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Met Glu Ser Asp
 115 120 125
 Asp Asp His Gly Val Lys Phe Arg Glu His Gln Phe Thr Lys Ile Asp
 130 135 140
 Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Met Asp Leu Gly Asp Arg
 145 150 155 160
 Ile Leu Lys Leu Asn Thr Glu Ile Arg Glu Val Gly Pro Val Asn Lys
 165 170 175
 Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Val Ala Leu
 180 185 190
 Val Ser Val Arg Val Tyr Phe Lys Lys Cys Pro Phe Thr Val Lys Asn
 195 200 205
 Leu Ala Met Phe Pro Asp Thr Val Pro Met Asp Ser Gln Ser Leu Val
 210 215 220
 Glu Val Arg Gly Ser Cys Val Asn Asn Ser Lys Glu Glu Asp Pro Pro
 225 230 235 240
 Arg Met Tyr Cys Ser Thr Glu Gly Glu Trp Leu Val Pro Ile Gly Lys
 245 250 255
 Cys Ser Cys Asn Ala Gly Tyr Glu Glu Arg Gly Phe Met Cys Gln Ala
 260 265 270
 Cys Arg Pro Gly Phe Tyr Lys Ala Leu Asp Gly Asn Met Lys Cys Ala
 275 280 285
 Lys Cys Pro Pro His Ser Ser Thr Gln Glu Asp Gly Ser Met Asn Cys
 290 295 300
 Arg Cys Glu Asn Asn Tyr Phe Arg Ala Asp Lys Asp Pro Pro Ser Met
 305 310 315 320

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Ala Cys Thr Arg Pro Pro Ser Ser Pro Arg Asn Val Ile Ser Asn Ile
 325 330 335
 Asn Glu Thr Ser Val Ile Leu Asp Trp Ser Trp Pro Leu Asp Thr Gly
 340 345 350
 Gly Arg Lys Asp Val Thr Phe Asn Ile Ile Cys Lys Lys Cys Gly Trp
 355 360 365
 Asn Ile Lys Gln Cys Glu Pro Cys Ser Pro Asn Val Arg Phe Leu Pro
 370 375 380
 Arg Gln Phe Gly Leu Thr Asn Thr Thr Val Thr Val Thr Asp Leu Leu
 385 390 395 400
 Ala His Thr Asn Tyr Thr Phe Glu Ile Asp Ala Val Asn Gly Val Ser
 405 410 415
 Glu Leu Ser Ser Pro Pro Arg Gln Phe Ala Ala Val Ser Ile Thr Thr
 420 425 430
 Asn Gln Ala Ala Pro Ser Pro Val Leu Thr Ile Lys Lys Asp Arg Thr
 435 440 445
 Ser Arg Asn Ser Ile Ser Leu Ser Trp Gln Glu Pro Glu His Pro Asn
 450 455 460
 Gly Ile Ile Leu Asp Tyr Glu Val Lys Tyr Tyr Glu Lys Gln Glu Gln
 465 470 475 480
 Glu Thr Ser Tyr Thr Ile Leu Arg Ala Arg Gly Thr Asn Val Thr Ile
 485 490 495
 Ser Ser Leu Lys Pro Asp Thr Ile Tyr Val Leu Gln Ile Arg Ala Arg
 500 505 510
 Thr Ala Ala Gly Tyr Gly Thr Asn Ser Arg Lys Phe Glu Phe Glu Thr
 515 520 525
 Ser Pro Asp Ser Phe Ser Ile Ser Gly Glu Ser Ser Gln Val Val Met
 530 535 540
 Ile Ala Ile Ser Ala Ala Val Ala Ile Ile Leu Leu Thr Val Val Ile
 545 550 555 560
 Tyr Val Leu Ile Gly Arg Phe Cys Gly Tyr Lys Ser Lys His Gly Ala
 565 570 575
 Asp Glu Lys Arg Leu His Phe Gly Asn Gly His Leu Lys Leu Pro Gly
 580 585 590
 Leu Arg Thr Tyr Val Asp Pro His Thr Tyr Glu Asp Pro Thr Gln Ala
 595 600 605
 Val His Glu Phe Ala Lys Glu Leu Asp Ala Thr Asn Ile Ser Ile Asp
 610 615 620

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Lys Val Val Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu
 625 630 635 640
 Lys Leu Pro Ser Lys Lys Glu Ile Ser Val Ala Ile Lys Thr Leu Lys
 645 650 655
 Val Gly Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Gly Glu Ala Ser
 660 665 670
 Ile Met Gly Gln Phe Asp His Pro Asn Ile Ile Arg Leu Glu Gly Val
 675 680 685
 Val Thr Lys Ser Lys Pro Val Met Ile Val Thr Glu Tyr Met Glu Asn
 690 695 700
 Gly Ser Leu Asp Ser Phe Leu Arg Lys His Asp Ala Gln Phe Thr Val
 705 710 715 720
 Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ser Gly Met Lys Tyr
 725 730 735
 Leu Ser Asp Met Gly Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile
 740 745 750
 Leu Ile Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser
 755 760 765
 Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly
 770 775 780
 Lys Ile Pro Ile Arg Trp Thr Ser Pro Glu Ala Ile Ala Tyr Arg Lys
 785 790 795 800
 Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Leu Trp Glu
 805 810 815
 Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Glu Met Ser Asn Gln Asp
 820 825 830
 Val Ile Lys Ala Val Asp Glu Gly Tyr Arg Leu Pro Pro Pro Met Asp
 835 840 845
 Cys Pro Ala Ala Leu Tyr Gln Leu Met Leu Asp Cys Trp Gln Lys Asp
 850 855 860
 Arg Asn Asn Arg Pro Lys Phe Glu Gln Ile Val Ser Ile Leu Asp Lys
 865 870 875 880
 Leu Ile Arg Asn Pro Gly Ser Leu Lys Ile Ile Thr Ser Ala Ala Ala
 885 890 895
 Arg Pro Ser Asn Leu Leu Leu Asp Gln Ser Asn Val Asp Ile Ser Thr
 900 905 910
 Phe Arg Thr Thr Gly Asp Trp Leu Asn Gly Val Arg Thr Ala His Cys
 915 920 925

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Lys Glu Ile Phe Thr Gly Val Glu Tyr Ser Ser Cys Asp Thr Ile Ala
930 935 940

Lys Ile Ser Thr Asp Asp Met Lys Lys Val Gly Val Thr Val Val Gly
945 950 955 960

Pro Gln Lys Lys Ile Ile Ser Ser Ile Lys Ala Leu Glu Thr Gln Ser
965 970 975

Lys Asn Gly Pro Val Pro Val
980

(2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CTGCTCGCCG CCGTGAAGA AACG

24

(2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GCGTCTAGAT TATCACTTCT CCTGGATGCT TGTCTGGTA

39

(2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GCGGACGCCG CCGCCATGGC CCTGGATTGC CTGCTGCTGT TCCTCCTG

48

(2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 54 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CGTTTCTTCC ACGGCGGCGA GCAGAGATGC CAGGAGGAAC AGCAGCAGGC AATC

54

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 13 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Met	Ala	Leu	Asp	Cys	Leu	Leu	Leu	Phe	Leu	Leu	Ala	Ser
1				5					10			

(2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 26 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

AGGGAATTCC AYCGNGAYYT NGCNGC

26

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(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 24 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: cDNA

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

AGGGGATCCR WARSWCCANA CRTC

24

WHAT IS CLAIMED IS:

1. An isolated nucleic acid encoding a polypeptide having at least one of the biological activities of an EPH-like receptor protein tyrosine kinase, the nucleic acid selected from the group consisting of:
 - (a) the nucleic acids set forth in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16 and their complementary strands;
 - (b) a nucleic acid hybridizing to the coding regions of the nucleic acids in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16; and
 - (c) a nucleic acid of (b) which, but for the degeneracy of the genetic code, would hybridize to the coding regions of the nucleic acids in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16.
2. A polypeptide product of expression of a nucleic acid of Claim 1 in a procaryotic or eucaryotic host cell.
3. A nucleic acid of Claim 1 which is of human origin.
4. A nucleic acid of Claim 1 which encodes a polypeptide having part or all of the amino acid sequence as shown in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16.
5. A nucleic acid of Claim 1 encoding a fragment comprising an EPH-like receptor extracellular domain.
6. A nucleic acid of Claim 1 which is cDNA, genomic DNA, synthetic DNA or RNA.

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7. A nucleic acid of Claim 1 which includes one or more codons preferred for expression in E. coli host cells.

5

8. A nucleic acid of Claim 1 which includes one or more codon preferred for expression in mammalian cells.

10

9. A nucleic acid encoding amino acids 6-524 as set forth in SEQ ID NO: 10, and optionally encoding an amino terminal methionyl residue.

15

10. A nucleic acid encoding amino acids 1-547 as set forth in SEQ ID NO: 12, and optionally encoding an amino acid terminal methionyl residue.

20

11. A nucleic acid encoding amino acids 21-547 as set forth in SEQ ID NO: 14, and optionally encoding an amino terminal methionyl residue.

25

12. A nucleic acid encoding amino acids 23-553 as set forth in SEQ ID NO: 16, and optionally encoding an amino terminal methionyl residue.

13. A nucleic acid encoding a chimeric protein, wherein the protein comprises an EPH-like receptor extracellular domain fused to a heterologous receptor cytoplasmic domain.

30

14. A nucleic acid of Claim 13 wherein the extracellular domain is selected from the group consisting of HEK5, HEK7, HEK8 and HEK11 extracellular domains.

35

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15. A biologically functional plasmid or viral DNA vector including a nucleic acid of Claim 1.

5 16. A procaryotic or eucaryotic host cell stably transformed or transfected with the plasmid of Claim 15.

10 17. A method of producing an EPH-like receptor protein tyrosine kinase comprising culturing the host cell of Claim 16 to allow the host cell to express the EPH-like receptor protein tyrosine kinase.

15 18. An isolated polypeptide having an amino acid sequence as shown in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16, or a fragment or analog thereof, wherein the polypeptide has at least one of the biological activities of an EPH-like receptor protein tyrosine kinase.

20 19. Purified and isolated HEK5 receptor.

20. Purified and isolated HEK7 receptor.

25 21. Purified and isolated HEK8 receptor.

22. Purified and isolated HEK11 receptor.

30 23. A polypeptide of Claim 18 wherein the biological activity is the binding of a ligand.

24. A polypeptide of Claim 18 which is of human origin.

35 25. A polypeptide of Claims 18 characterized by being the product of procaryotic or eucaryotic expression of an exogenous DNA sequence.

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26. A polypeptide of Claim 25 wherein the exogenous DNA is a cDNA.

5 27. A polypeptide of Claim 25 wherein the exogenous DNA is a genomic DNA.

28. An antibody or fragment thereof specifically binding a polypeptide of Claim 18.

10

29. An antibody of Claim 28 which is a monoclonal antibody.

15 30. A pharmaceutical composition comprising a therapeutically effective amount of a polypeptide of Claim 18 in a mixture with a pharmaceutically acceptable adjuvant, carrier, solubilizer or diluent.

20 31. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of Claim 28 in a mixture with a pharmaceutically acceptable adjuvant, carrier, solubilizer or diluent.

25 32. A method for modulating the endogenous activation of an EPH-like receptor protein tyrosine kinase comprising administering an effective amount of a polypeptide of Claim 18.

30 33. A method for modulating the synthesis of an EPH-like receptor protein tyrosine kinase comprising hybridizing an antisense oligonucleotide to a nucleic acid of Claim 1.

5 a) exposing at least one molecule to the receptor polypeptide for a time sufficient to allow formation of a receptor/ligand complex;

b) removing non-complexed molecules; and

c) detecting the presence of the molecule bound to the receptor polypeptide.

10

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FIG. 1A

CTG	CTC	GCC	GCC	GTG	GAA	GAA	ACG	CTA	ATG	GAC	TCC	ACT	ACA	GCG	ACT	48
Leu	Leu	Ala	Ala	Val	Glu	Glu	Thr	Leu	Met	Asp	Ser	Thr	Thr	Ala	Thr	
1				5					10					15		
GCT	GAG	CTG	GGC	TGG	ATG	GTG	CAT	CCT	CCA	TCA	GGG	TGG	GAA	GAG	GTG	96
Ala	Glu	Leu	Gly	Trp	Met	Val	His	Pro	Pro	Ser	Gly	Trp	Glu	Glu	Val	
			20					25					30			
AGT	GGC	TAC	GAT	GAG	AAC	ATG	AAC	ACG	ATC	CGC	ACG	TAC	CAG	GTG	TGC	144
Ser	Gly	Tyr	Asp	Glu	Asn	Met	Asn	Thr	Ile	Arg	Thr	Tyr	Gln	Val	Cys	
		35					40					45				
AAC	GTG	TTT	GAG	TCA	AGC	CAG	AAC	AAC	TGG	CTA	CGG	ACC	AAG	TTT	ATC	192
Asn	Val	Phe	Glu	Ser	Ser	Gln	Asn	Asn	Trp	Leu	Arg	Thr	Lys	Phe	Ile	
	50					55					60					
CGG	CGC	CGT	GGG	GCC	CAC	CGC	ATC	CAC	GTG	GAG	ATG	AAG	TTT	TCG	GTG	240
Arg	Arg	Arg	Gly	Ala	His	Arg	Ile	His	Val	Glu	Met	Lys	Phe	Ser	Val	
65					70				75					80		
CGT	GAC	TGC	AGC	AGC	ATC	CCC	AGC	GTG	CCT	GGC	TCC	TGC	AAG	GAG	ACC	288
Arg	Asp	Cys	Ser	Ser	Ile	Pro	Ser	Val	Pro	Gly	Ser	Cys	Lys	Glu	Thr	
				85				90						95		
TTC	AAC	CTC	TAT	TAC	TAT	GAG	GCT	GAC	TTT	GAC	TCG	GCC	ACC	AAG	ACC	336
Phe	Asn	Leu	Tyr	Tyr	Tyr	Glu	Ala	Asp	Phe	Asp	Ser	Ala	Thr	Lys	Thr	
			100					105					110			
TTC	CCC	AAC	TGG	ATG	GAG	AAT	CCA	TGG	GTG	AAG	GTG	GAT	ACC	ATT	GCA	384
Phe	Pro	Asn	Trp	Met	Glu	Asn	Pro	Trp	Val	Lys	Val	Asp	Thr	Ile	Ala	
		115					120					125				
GCC	GAC	GAG	AGC	TTC	TCC	CAG	GTG	GAC	CTG	GGT	GGC	CGC	GTC	ATG	AAA	432
Ala	Asp	Glu	Ser	Phe	Ser	Gln	Val	Asp	Leu	Gly	Gly	Arg	Val	Met	Lys	
		130				135					140					
ATC	AAC	ACC	GAG	GTG	CGG	AGC	TTC	GGA	CCT	GTG	TCC	CGC	AGC	GGC	TTC	480
Ile	Asn	Thr	Glu	Val	Arg	Ser	Phe	Gly	Pro	Val	Ser	Arg	Ser	Gly	Phe	
145					150				155					160		
TAC	CTG	GCC	TTC	CAG	GAC	TAT	GGC	GGC	TGC	ATG	TCC	CTC	ATC	GCC	GTG	528
Tyr	Leu	Ala	Phe	Gln	Asp	Tyr	Gly	Gly	Cys	Met	Ser	Leu	Ile	Ala	Val	
				165				170						175		
CGT	GTC	TTC	TAC	CGC	AAG	TGC	CCC	CGC	ATC	ATC	CAG	AAT	GGC	GCC	ATC	576
Arg	Val	Phe	Tyr	Arg	Lys	Cys	Pro	Arg	Ile	Ile	Gln	Asn	Gly	Ala	Ile	
			180					185					190			

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FIG. 1B

TTC CAG GAA ACC CTG TCG GGG GCT GAG AGC ACA TCG CTG GTG GCT GCC Phe Gln Glu Thr Leu Ser Gly Ala Glu Ser Thr Ser Leu Val Ala Ala 195 200 205	624
CGG GGC AGC TGC ATC GCC AAT GCG GAA GAG GTG GAT GTA CCC ATC AAG Arg Gly Ser Cys Ile Ala Asn Ala Glu Glu Val Asp Val Pro Ile Lys 210 215 220	672
CTC TAC TGT AAC GGG GAC GGC GAG TGG CTG GTG CCC ATC GGG CGC TGC Leu Tyr Cys Asn Gly Asp Gly Glu Trp Leu Val Pro Ile Gly Arg Cys 225 230 235 240	720
ATG TGC AAA GCA GGC TTC GAG GCC GTT GAG AAT GGC ACC GTC TGC CGA Met Cys Lys Ala Gly Phe Glu Ala Val Glu Asn Gly Thr Val Cys Arg 245 250 255	768
GGT TGT CCA TCT GGG ACT TTC AAG GCC AAC CAA GGG GAT GAG GCC TGT Gly Cys Pro Ser Gly Thr Phe Lys Ala Asn Gln Gly Asp Glu Ala Cys 260 265 270	816
ACC CAC TGT CCC ATC AAC AGC CGG ACC ACT TCT GAA GGG GCC ACC AAC Thr His Cys Pro Ile Asn Ser Arg Thr Thr Ser Glu Gly Ala Thr Asn 275 280 285	864
TGT GTC TGC CGC AAT GGC TAC TAC AGA GCA GAC CTG GAC CCC CTG GAC Cys Val Cys Arg Asn Gly Tyr Tyr Arg Ala Asp Leu Asp Pro Leu Asp 290 295 300	912
ATG CCC TGC ACA ACC ATC CCC TCC GCG CCC CAG GCT GTG ATT TCC AGT Met Pro Cys Thr Thr Ile Pro Ser Ala Pro Gln Ala Val Ile Ser Ser 305 310 315 320	960
GTC AAT GAG ACC TCC CTC ATG CTG GAG TGG ACC CCT CCC CGC GAC TCC Val Asn Glu Thr Ser Leu Met Leu Glu Trp Thr Pro Pro Arg Asp Ser 325 330 335	1008
GGA GGC CGA GAG GAC CTC GTC TAC AAC ATC ATC TGC AAG AGC TGT GGC Gly Gly Arg Glu Asp Leu Val Tyr Asn Ile Ile Cys Lys Ser Cys Gly 340 345 350	1056
TCG GGC CGG GGT GCC TGC ACC CGC TGC GGG GAC AAT GTA CAG TAC GCA Ser Gly Arg Gly Ala Cys Thr Arg Cys Gly Asp Asn Val Gln Tyr Ala 355 360 365	1104
CCA CGC CAG CTA GGC CTG ACC GAG CCA CGC ATT TAC ATC AGT GAC CTG Pro Arg Gln Leu Gly Leu Thr Glu Pro Arg Ile Tyr Ile Ser Asp Leu 370 375 380	1152
CTG GCC CAC ACC CAG TAC ACC TTC GAG ATC CAG GCT GTG AAC GGC GTT Leu Ala His Thr Gln Tyr Thr Phe Glu Ile Gln Ala Val Asn Gly Val 385 390 395 400	1200

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FIG. 1C

ACT GAC CAG AGC CCC TTC TCG CCT CAG TTC GCC TCT GTG AAC ATC ACC	1248
Thr Asp Gln Ser Pro Phe Ser Pro Gln Phe Ala Ser Val Asn Ile Thr	
405 410 415	
ACC AAC CAG GCA GCT CCA TCG GCA GTG TCC ATC ATG CAT CAG GTG AGC	1296
Thr Asn Gln Ala Ala Pro Ser Ala Val Ser Ile Met His Gln Val Ser	
420 425 430	
CGC ACC GTG GAC AGC ATT ACC CTG TCG TGG TCC CAG CCG GAC CAG CCC	1344
Arg Thr Val Asp Ser Ile Thr Leu Ser Trp Ser Gln Pro Asp Gln Pro	
435 440 445	
AAT GGC GTG ATC CTG GAC TAT GAG CTG CAG TAC TAT GAG AAG GAG CTC	1392
Asn Gly Val Ile Leu Asp Tyr Glu Leu Gln Tyr Tyr Glu Lys Glu Leu	
450 455 460	
AGT GAG TAC AAC GCC ACA GCC ATA AAA AGC CCC ACC AAC ACG GTC ACG	1440
Ser Glu Tyr Asn Ala Thr Ala Ile Lys Ser Pro Thr Asn Thr Val Thr	
465 470 475 480	
GGC CTC AAA GCC GGC GCC ATC TAT GTC TTC CAG GTG CGG GCA CGC ACT	1488
Gly Leu Lys Ala Gly Ala Ile Tyr Val Phe Gln Val Arg Ala Arg Thr	
485 490 495	
GTG GCA GGC TAC GGG CGC TAC AGC GGC AAG ATG TAC TTC CAG ACC ATG	1536
Val Ala Gly Tyr Gly Arg Tyr Ser Gly Lys Met Tyr Phe Gln Thr Met	
500 505 510	
ACA GAA GCC GAG TAC CAG ACA AGC ATC CAG GAG AAG TTG CCA CTC ATC	1584
Thr Glu Ala Glu Tyr Gln Thr Ser Ile Gln Glu Lys Leu Pro Leu Ile	
515 520 525	
ATC GGC TCC TCG GCC GCT GGC CTG GTC TTC CTC ATT GCT GTG GTT GTC	1632
Ile Gly Ser Ser Ala Ala Gly Leu Val Phe Leu Ile Ala Val Val Val	
530 535 540	
ATC GCC ATC GTG TGT AAC AGA CGG GGG TTT GAG CGT GCT GAC TCG GAG	1680
Ile Ala Ile Val Cys Asn Arg Arg Gly Phe Glu Arg Ala Asp Ser Glu	
545 550 555 560	
TAC ACG GAC AAG CTG CAA CAC TAC ACC AGT GGC CAC ATA ACC CCA GGC	1728
Tyr Thr Asp Lys Leu Gln His Tyr Thr Ser Gly His Ile Thr Pro Gly	
565 570 575	
ATG AAG ATC TAC ATC GAT CCT TTC ACC TAC GAG GAC CCC AAC GAG GCA	1776
Met Lys Ile Tyr Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn Glu Ala	
580 585 590	
GTG CGG GAG TTT GCC AAG GAA ATT GAC ATC TCC TGT GTC AAA ATT GAG	1824
Val Arg Glu Phe Ala Lys Glu Ile Asp Ile Ser Cys Val Lys Ile Glu	
595 600 605	

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FIG. ID

CAG GTG ATC GGA GCA GGG GAG TTT GGC GAG GTC TGC AGT GGC CAC CTG Gln Val Ile Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly His Leu 610 615 620	1872
AAG CTG CCA GGC AAG AGA GAG ATC TTT GTG GCC ATC AAG ACG CTC AAG Lys Leu Pro Gly Lys Arg Glu Ile Phe Val Ala Ile Lys Thr Leu Lys 625 630 635 640	1920
TCG GGC TAC ACG GAG AAG CAG CGC CGG GAC TTC CTG AGC GAA GCC TCC Ser Gly Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser 645 650 655	1968
ATC ATG GGC CAG TTC GAC CAT CCC AAC GTC ATC CAC CTG GAG GGT GTC Ile Met Gly Gln Phe Asp His Pro Asn Val Ile His Leu Glu Gly Val 660 665 670	2016
GTG ACC AAG AGC ACA CCT GTG ATG ATC ATC ACC GAG TTC ATG GAG AAT Val Thr Lys Ser Thr Pro Val Met Ile Ile Thr Glu Phe Met Glu Asn 675 680 685	2064
GGC TCC CTG GAC TCC TTT CTC CGG CAA AAC GAT GGG CAG TTC ACA GTC Gly Ser Leu Asp Ser Phe Leu Arg Gln Asn Asp Gly Gln Phe Thr Val 690 695 700	2112
ATC CAG CTG GTG GGC ATG CTT CGG GGC ATC GCA GCT GGC ATG AAG TAC Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ala Gly Met Lys Tyr 705 710 715 720	2160
CTG GCA GAC ATG AAC TAT GTT CAC CGT GAC CTG GCT GCC CGC AAC ATC Leu Ala Asp Met Asn Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile 725 730 735	2208
CTC GTC AAC AGC AAC CTG GTC TGC AAG GTG TCG GAC TTT GGG CTC TCA Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser 740 745 750	2256
CGC TTT CTA GAG GAC GAT ACC TCA GAC CCC ACC TAC ACC AGT GCC CTG Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro Thr Tyr Thr Ser Ala Leu 755 760 765	2304
GGC GGA AAG TTC CCC ATC CGC TGG ACA GCC CCG GAA GCC ATC CAG TAC Gly Gly Lys Phe Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr 770 775 780	2352
CGG AAG TTC ACC TCG GCC AGT GAT GTG TGG AGC TAC GGC ATT GTC ATG Arg Lys Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met 785 790 795 800	2400
TGG GAG GTG ATG TCC TAT GGG GAG CGG CCC TAC TGG GAC ATG ACC AAC Trp Glu Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Thr Asn 805 810 815	2448

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FIG. 1E

CAG GAT GTA ATC AAT GCC ATT GAG CAG GAC TAT CGG CTG CCA CCG CCC Gln Asp Val Ile Asn Ala Ile Glu Gln Asp Tyr Arg Leu Pro Pro Pro 820 825 830	2496
ATG GAC TGC CCG AGC GCC CTG CAC CAA CTC ATG CTG GAC TGT TGG CAG Met Asp Cys Pro Ser Ala Leu His Gln Leu Met Leu Asp Cys Trp Gln 835 840 845	2544
AAG GAC CGC AAC CAC CGG CCC AAG TTC GGC CAA ATT GTC AAC ACG CTA Lys Asp Arg Asn His Arg Pro Lys Phe Gly Gln Ile Val Asn Thr Leu 850 855 860	2592
GAC AAG ATG ATC CGC AAT CCC AAC AGC CTC AAA GCC ATG GCG CCC CTC Asp Lys Met Ile Arg Asn Pro Asn Ser Leu Lys Ala Met Ala Pro Leu 865 870 875 880	2640
TCC TCT GGC ATC AAC CTG CCG CTG CTG GAC CGC ACG ATC CCC GAC TAC Ser Ser Gly Ile Asn Leu Pro Leu Leu Asp Arg Thr Ile Pro Asp Tyr 885 890 895	2688
ACC AGC TTT AAC ACG GTG GAC GAG TGG CTG GAG GCC ATC AAG ATG GGG Thr Ser Phe Asn Thr Val Asp Glu Trp Leu Glu Ala Ile Lys Met Gly 900 905 910	2736
CAG TAC AAG GAG AGC TTC GCC AAT GCC GGC TTC ACC TCC TTT GAC GTC Gln Tyr Lys Glu Ser Phe Ala Asn Ala Gly Phe Thr Ser Phe Asp Val 915 920 925	2784
GTG TCT CAG ATG ATG ATG GAG GAC ATT CTC CGG GTT GGG GTC ACT TTG Val Ser Gln Met Met Met Glu Asp Ile Leu Arg Val Gly Val Thr Leu 930 935 940	2832
GCT GGC CAC CAG AAA AAA ATC CTG AAC AGT ATC CAG GTG ATG CCG GCG Ala Gly His Gln Lys Lys Ile Leu Asn Ser Ile Gln Val Met Arg Ala 945 950 955 960	2880
CAG ATG AAC CAG ATT CAG TCT GTG GAG GTT TGACATTAC CTGCCTCGGC Gln Met Asn Gln Ile Gln Ser Val Glu Val 965 970	2930
TCACCTCTTC CTCCAAGCCC CGCCCCCTCT GC	2962

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FIG. 2A

CCA GCG TCC CTG GCC GGC TGC TAC TCT GCA CCT CGA CGG GCT CCC CTC	48
Pro Ala Ser Leu Ala Gly Cys Tyr Ser Ala Pro Arg Arg Ala Pro Leu	
1 5 10 15	
TGG ACG TGC CTT CTC CTG TGC GCC GCA CTC CGG ACC CTC CTG GCC AGC	96
Trp Thr Cys Leu Leu Leu Cys Ala Ala Leu Arg Thr Leu Leu Ala Ser	
20 25 30	
CCC AGC AAC GAA GTG AAT TTA TTG GAT TCA CGC ACT GTC ATG GGG GAC	144
Pro Ser Asn Glu Val Asn Leu Leu Asp Ser Arg Thr Val Met Gly Asp	
35 40 45	
CTG GGA TGG ATT GCT TTT CCA AAA AAT GGG TGG GAA GAG ATT GGT GAA	192
Leu Gly Trp Ile Ala Phe Pro Lys Asn Gly Trp Glu Glu Ile Gly Glu	
50 55 60	
GTG GAT GAA AAT TAT GCC CCT ATC CAC ACA TAC CAA GTA TGC AAA GTG	240
Val Asp Glu Asn Tyr Ala Pro Ile His Thr Tyr Gln Val Cys Lys Val	
65 70 75 80	
ATG GAA CAG AAT CAG AAT AAC TGG CTT TTG ACC AGT TGG ATC TCC AAT	288
Met Glu Gln Asn Gln Asn Asn Trp Leu Leu Thr Ser Trp Ile Ser Asn	
85 90 95	
GAA GGT GCT TCC AGA ATC TTC ATA GAA CTC AAA TTT ACC CTG CGG GAC	336
Glu Gly Ala Ser Arg Ile Phe Ile Glu Leu Lys Phe Thr Leu Arg Asp	
100 105 110	
TGC AAC AGC CTT CCT GGA GGA CTG GGG ACC TGT AAG GAA ACC TTT AAT	384
Cys Asn Ser Leu Pro Gly Gly Leu Gly Thr Cys Lys Glu Thr Phe Asn	
115 120 125	
ATG TAT TAC TTT GAG TCA GAT GAT CAG AAT GGG AGA AAC ATC AAG GAA	432
Met Tyr Tyr Phe Glu Ser Asp Asp Gln Asn Gly Arg Asn Ile Lys Glu	
130 135 140	
AAC CAA TAC ATC AAA ATT GAT ACC ATT GCT GCC GAT GAA AGC TTT ACA	480
Asn Gln Tyr Ile Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr	
145 150 155 160	
GAA CTT GAT CTT GGT GAC CGT GTT ATG AAA CTG AAT ACA GAG GTC AGA	528
Glu Leu Asp Leu Gly Asp Arg Val Met Lys Leu Asn Thr Glu Val Arg	
165 170 175	
GAT GTA GGA CCT CTA AGC AAA AAG GGA TTT TAT CTT GCT TTT CAA GAT	576
Asp Val Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp	
180 185 190	
GTT GGT GCT TGC ATT GCT CTG GTT TCT GTG CGT GTA TAC TAT AAA AAA	624
Val Gly Ala Cys Ile Ala Leu Val Ser Val Arg Val Tyr Tyr Lys Lys	
195 200 205	

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FIG. 2B

TGC CCT TCT GTG GTA CGA CAC TTG GCT GTC TTC CCT GAC ACC ATC ACT	672
Cys Pro Ser Val Val Arg His Leu Ala Val Phe Pro Asp Thr Ile Thr	
210 215 220	
GGA GCT GAT TCT TCC CAA TTG CTC GAA GTG TCG GGC TCC TGT GTC AAC	720
Gly Ala Asp Ser Ser Gln Leu Leu Glu Val Ser Gly Ser Cys Val Asn	
225 230 235 240	
CAT TCT GTG ACC GAT GAA CCT CCC AAA ATG CAC TGC AGC GCC GAA GGG	768
His Ser Val Thr Asp Glu Pro Pro Lys Met His Cys Ser Ala Glu Gly	
245 250 255	
GAG TGG CTG GTG CCC ATC GGG AAA TGC ATG TGC AAG GCA GGA TAT GAA	816
Glu Trp Leu Val Pro Ile Gly Lys Cys Met Cys Lys Ala Gly Tyr Glu	
260 265 270	
GAG AAA AAT GGC ACC TGT CAA GTG TGC AGA CCT GGG TTC TTC AAA GCC	864
Glu Lys Asn Gly Thr Cys Gln Val Cys Arg Pro Gly Phe Phe Lys Ala	
275 280 285	
TCA CCT CAC ATC CAG AGC TGC GGC AAA TGT CCA CCT CAC AGT TAT ACC	912
Ser Pro His Ile Gln Ser Cys Gly Lys Cys Pro Pro His Ser Tyr Thr	
290 295 300	
CAT GAG GAA GCT TCA ACC TCT TGT GTC TGT GAA AAG GAT TAT TTC AGG	960
His Glu Glu Ala Ser Thr Ser Cys Val Cys Glu Lys Asp Tyr Phe Arg	
305 310 315 320	
AGA GAG TCT GAT CCA CCC ACA ATG GCA TGC ACA AGA CCC CCC TCT GCT	1008
Arg Glu Ser Asp Pro Pro Thr Met Ala Cys Thr Arg Pro Pro Ser Ala	
325 330 335	
CCT CGG AAT GCC ATC TCA AAT GTT AAT GAA ACT AGT GTC TTT CTG GAA	1056
Pro Arg Asn Ala Ile Ser Asn Val Asn Glu Thr Ser Val Phe Leu Glu	
340 345 350	
TGG ATT CCG CCT GCT GAC ACT GGT GGA AGG AAA GAC GTG TCA TAT TAT	1104
Trp Ile Pro Pro Ala Asp Thr Gly Gly Arg Lys Asp Val Ser Tyr Tyr	
355 360 365	
ATT GCA TGC AAG AAG TGC AAC TCC CAT GCA GGT GTG TGT GAG GAG TGT	1152
Ile Ala Cys Lys Lys Cys Asn Ser His Ala Gly Val Cys Glu Glu Cys	
370 375 380	
GGC GGT CAT GTC AGG TAC CTT CCC CGG CAA AGC GGC CTG AAA AAC ACC	1200
Gly Gly His Val Arg Tyr Leu Pro Arg Gln Ser Gly Leu Lys Asn Thr	
385 390 395 400	
TCT GTC ATG ATG GTG GAT CTA CTC GCT CAC ACA AAC TAT ACC TTT GAG	1248
Ser Val Met Met Val Asp Leu Leu Ala His Thr Asn Tyr Thr Phe Glu	
405 410 415	

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FIG. 2C

ATT GAG GCA GTG AAT GGA GTG TCC GAC TTG AGC CCA GGA GCC CGG CAG Ile Glu Ala Val Asn Gly Val Ser Asp Leu Ser Pro Gly Ala Arg Gln 420 425 430	1296
TAT GTG TCT GTA AAT GTA ACC ACA AAT CAA GCA GCT CCA TCT CCA GTG Tyr Val Ser Val Asn Val Thr Thr Asn Gln Ala Ala Pro Ser Pro Val 435 440 445	1344
ACC AAT GTG AAA AAA GGG AAA ATT GCA AAA AAC AGC ATC TCT TTG TCT Thr Asn Val Lys Lys Gly Lys Ile Ala Lys Asn Ser Ile Ser Leu Ser 450 455 460	1392
TGG CAA GAA CCA GAT CGT CCC AAT GGA ATC ATC CTA GAG TAT GAA ATC Trp Gln Glu Pro Asp Arg Pro Asn Gly Ile Ile Leu Glu Tyr Glu Ile 465 470 475 480	1440
AAG CAT TTT GAA AAG GAC CAA GAG ACC AGC TAC ACG ATT ATC AAA TCT Lys His Phe Glu Lys Asp Gln Glu Thr Ser Tyr Thr Ile Ile Lys Ser 485 490 495	1488
AAA GAG ACA ACT ATT ACT GCA GAG GGC TTG AAA CCA GCT TCA GTT TAT Lys Glu Thr Thr Ile Thr Ala Glu Gly Leu Lys Pro Ala Ser Val Tyr 500 505 510	1536
GTC TTC CAA ATT CGA GCA CGT ACA GCA GCA GGC TAT GGT GTC TTC AGT Val Phe Gln Ile Arg Ala Arg Thr Ala Ala Gly Tyr Gly Val Phe Ser 515 520 525	1584
CGA AGA TTT GAG TTT GAA ACC ACC CCA GTG TTT GCA GCA TCC AGC GAT Arg Arg Phe Glu Phe Glu Thr Thr Pro Val Phe Ala Ala Ser Ser Asp 530 535 540	1632
CAA AGC CAG ATT CCT GTA ATT GCT GTG TCT GTG ACA GTA GGA GTC ATT Gln Ser Gln Ile Pro Val Ile Ala Val Ser Val Thr Val Gly Val Ile 545 550 555 560	1680
TTG TTG GCA GTG GTT ATC GGC GTC CTC CTC AGT GGA AGG CGG TGT GGC Leu Leu Ala Val Val Ile Gly Val Leu Leu Ser Gly Arg Arg Cys Gly 565 570 575	1728
TAC AGC AAA GCA AAA CAA GAT CCA GAA GAG GAA AAG ATG CAT TTT CAT Tyr Ser Lys Ala Lys Gln Asp Pro Glu Glu Glu Lys Met His Phe His 580 585 590	1776
AAT GGG CAC ATT AAA CTG CCA GGA GTA AGA ACT TAC ATT GAT CCA CAT Asn Gly His Ile Lys Leu Pro Gly Val Arg Thr Tyr Ile Asp Pro His 595 600 605	1824
ACC TAT GAG GAT CCC AAT CAA GCT GTC CAC GAA TTT GCC AAG GAG ATA Thr Tyr Glu Asp Pro Asn Gln Ala Val His Glu Phe Ala Lys Glu Ile 610 615 620	1872

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FIG. 2D

GAA GCA TCA TGT ATC ACC ATT GAG AGA GTT ATT GGA GCA GGT GAA TTT	1920
Glu Ala Ser Cys Ile Thr Ile Glu Arg Val Ile Gly Ala Gly Glu Phe	
625 630 635 640	
GGT GAA GTT TGT AGT GGA CGT TTG AAA CTA CCA GGA AAA AGA GAA TTA	1968
Gly Glu Val Cys Ser Gly Arg Leu Lys Leu Pro Gly Lys Arg Glu Leu	
645 650 655	
CCT GTG GCT ATC AAA ACC CTT AAA GTA GGC TAT ACT GAA AAG CAA CGC	2016
Pro Val Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr Glu Lys Gln Arg	
660 665 670	
AGA GAT TTC CTA GGT GAA GCA AGT ATC ATG GGA CAG TTT GAT CAT CCT	2064
Arg Asp Phe Leu Gly Glu Ala Ser Ile Met Gly Gln Phe Asp His Pro	
675 680 685	
AAC ATC ATC CAT TTA GAA GGT GTG GTG ACC AAA AGT AAA CCA GTG ATG	2112
Asn Ile Ile His Leu Glu Gly Val Val Thr Lys Ser Lys Pro Val Met	
690 695 700	
ATC GTG ACA GAG TAT ATG GAG AAT GGC TCT TTA GAT ACA TTT TTG AAG	2160
Ile Val Thr Glu Tyr Met Glu Asn Gly Ser Leu Asp Thr Phe Leu Lys	
705 710 715 720	
AAA AAC GAT GGG CAG TTC ACT GTG ATT CAG CTT GTT GGC ATG CTG AGA	2208
Lys Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val Gly Met Leu Arg	
725 730 735	
GGT ATC TCT GCA GGA ATG AAG TAC CTT TCT GAC ATG GGC TAT GTG CAT	2256
Gly Ile Ser Ala Gly Met Lys Tyr Leu Ser Asp Met Gly Tyr Val His	
740 745 750	
AGA GAT CTT GCT GCC AGA AAC ATC TTA ATC AAC AGT AAC CTT GTG TGC	2304
Arg Asp Leu Ala Ala Arg Asn Ile Leu Ile Asn Ser Asn Leu Val Cys	
755 760 765	
AAA GTG TCT GAC TTT GGA CTT TCC CGG GTA CTG GAA GAT GAT CCC GAG	2352
Lys Val Ser Asp Phe Gly Leu Ser Arg Val Leu Glu Asp Asp Pro Glu	
770 775 780	
GCA GCC TAC ACC ACA AGG GGA GGA AAA ATT CCA ATC AGA TGG ACT GCC	2400
Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala	
785 790 795 800	
CCA GAA GCA ATA GCT TTC CGA AAG TTT ACT TCT GCC AGT GAT GTC TGG	2448
Pro Glu Ala Ile Ala Phe Arg Lys Phe Thr Ser Ala Ser Asp Val Trp	
805 810 815	
AGT TAT GGA ATA GTA ATG TGG GAA GTT GTG TCT TAT GGA GAG AGA CCC	2496
Ser Tyr Gly Ile Val Met Trp Glu Val Val Ser Tyr Gly Glu Arg Pro	
820 825 830	

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TAC TGG GAG ATG ACC AAT CAA GAT GTG ATT AAA GCG GTA GAG GAA GGC Tyr Trp Glu Met Thr Asn Gln Asp Val Ile Lys Ala Val Glu Glu Gly 835 840 845	2544
TAT CGT CTG CCA AGC CCC ATG GAT TGT CCT GCT GCT CTC TAT CAG TTA Tyr Arg Leu Pro Ser Pro Met Asp Cys Pro Ala Ala Leu Tyr Gln Leu 850 855 860	2592
ATG CTG GAT TGC TGG CAG AAA GAG CGA AAT AGC AGG CCC AAG TTT GAT Met Leu Asp Cys Trp Gln Lys Glu Arg Asn Ser Arg Pro Lys Phe Asp 865 870 875 880	2640
GAA ATA GTC AAC ATG TTG GAC AAG CTG ATA CGT AAC CCA AGT AGT CTG Glu Ile Val Asn Met Leu Asp Lys Leu Ile Arg Asn Pro Ser Ser Leu 885 890 895	2688
AAG ACG CTG GTT AAT GCA TCC TGC AGA GTA TCT AAT TTA TTG GCA GAA Lys Thr Leu Val Asn Ala Ser Cys Arg Val Ser Asn Leu Leu Ala Glu 900 905 910	2736
CAT AGC CCA CTA GGA TCT GGG GCC TAC AGA TCA GTA GGT GAA TGG CTA His Ser Pro Leu Gly Ser Gly Ala Tyr Arg Ser Val Gly Glu Trp Leu 915 920 925	2784
GAG GCA ATC AAG ATG GGC CGG TAT ACA GAG ATT TTC ATG GAA AAT GGA Glu Ala Ile Lys Met Gly Arg Tyr Thr Glu Ile Phe Met Glu Asn Gly 930 935 940	2832
TAC AGT TCA ATG GAC GCT GTG GCT CAG GTG ACC TTG GAG GAT TTG AGA Tyr Ser Ser Met Asp Ala Val Ala Gln Val Thr Leu Glu Asp Leu Arg 945 950 955 960	2880
CGG CTT GGA GTG ACT CTT GTC GGT CAC CAG AAG AAG ATC ATG AAC AGC Arg Leu Gly Val Thr Leu Val Gly His Gln Lys Lys Ile Met Asn Ser 965 970 975	2928
CTT CAA GAA ATG AAG GTG CAG CTG GTA AAC GGA ATG GTG CCA TTG TAACTTCATG 2983 Leu Gln Glu Met Lys Val Gln Leu Val Asn Gly Met Val Pro Leu 980 985 990	
TAAATGTCGC TTCTTCAAGT GAATGATTCT GCACTTTGTA AACAGCACTG AGATTTATTT	3043
TAACAAAAAA AGGGGGAAAA GGGAAAACAG TGATTTCTAA ACCTTAGAAA ACATTTGCCT	3103
CAGCCACAGA ATTTGTAATC ATGGTTTAC TGAAGTATCC AGTTCTTAGT CCTTAGTCT	3162

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FIG. 3A

AAGCGGCAGG AGCAGCGTTG GCACCGGCGA ACC ATG GCT GGG ATT TTC TAT TTC	54
Met Ala Gly Ile Phe Tyr Phe	
1 5	
GCC CTA TTT TCG TGT CTC TTC GGG ATT TGC GAC GCT GTC ACA GGT TCC	102
Ala Leu Phe Ser Cys Leu Phe Gly Ile Cys Asp Ala Val Thr Gly Ser	
10 15 20	
AGG GTA TAC CCC GCG AAT GAA GTT ACC TTA TTG GAT TCC AGA TCT GTT	150
Arg Val Tyr Pro Ala Asn Glu Val Thr Leu Leu Asp Ser Arg Ser Val	
25 30 35	
CAG GGA GAA CTT GGG TGG ATA GCA AGC CCT CTG GAA GGA GGG TGG GAG	198
Gln Gly Glu Leu Gly Trp Ile Ala Ser Pro Leu Glu Gly Gly Trp Glu	
40 45 50 55	
GAA GTG AGT ATC ATG GAT GAA AAA AAT ACA CCA ATC CGA ACC TAC CAA	246
Glu Val Ser Ile Met Asp Glu Lys Asn Thr Pro Ile Arg Thr Tyr Gln	
60 65 70	
GTG TGC AAT GTG ATG GAA CCC AGC CAG AAT AAC TGG CTA CGA ACT GAT	294
Val Cys Asn Val Met Glu Pro Ser Gln Asn Asn Trp Leu Arg Thr Asp	
75 80 85	
TGG ATC ACC CGA GAA GGG GCT CAG AGG GTG TAT ATT GAG ATT AAA TTC	342
Trp Ile Thr Arg Glu Gly Ala Gln Arg Val Tyr Ile Glu Ile Lys Phe	
90 95 100	
ACC TTG AGG GAC TGC AAT AGT CTT CCG GGC GTC ATG GGG ACT TGC AAG	390
Thr Leu Arg Asp Cys Asn Ser Leu Pro Gly Val Met Gly Thr Cys Lys	
105 110 115	
GAG ACG TTT AAC CTG TAC TAC TAT GAA TCA GAC AAC GAC AAA GAG CGT	438
Glu Thr Phe Asn Leu Tyr Tyr Tyr Glu Ser Asp Asn Asp Lys Glu Arg	
120 125 130 135	
TTC ATC AGA GAG AAC CAG TTT GTC AAA ATT GAC ACC ATT GCT GCT GAT	486
Phe Ile Arg Glu Asn Gln Phe Val Lys Ile Asp Thr Ile Ala Ala Asp	
140 145 150	
GAG AGC TTC ACC CAA GTG GAC ATT GGT GAC AGA ATC ATG AAG CTG AAC	534
Glu Ser Phe Thr Gln Val Asp Ile Gly Asp Arg Ile Met Lys Leu Asn	
155 160 165	
ACC GAG ATC CGG GAT GTA GGG CCA TTA AGC AAA AAG GGG TTT TAC CTG	582
Thr Glu Ile Arg Asp Val Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu	
170 175 180	

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FIG. 3B

GCT TTT CAG GAT GTG GGG GCC TGC ATC GCC CTG GTA TCA GTC CGT GTG Ala Phe Gln Asp Val Gly Ala Cys Ile Ala Leu Val Ser Val Arg Val 185 190 195	630
TTC TAT AAA AAG TGT CCA CTC ACA GTC CGC AAT CTG GCC CAG TTT CCT Phe Tyr Lys Lys Cys Pro Leu Thr Val Arg Asn Leu Ala Gln Phe Pro 200 205 210 215	678
GAC ACC ATC ACA GGG GCT GAT ACG TCT TCC CTG GTG GAA GTT CGA GGC Asp Thr Ile Thr Gly Ala Asp Thr Ser Ser Leu Val Glu Val Arg Gly 220 225 230	726
TCC TGT GTC AAC AAC TCA GAA GAG AAA GAT GTG CCA AAA ATG TAC TGT Ser Cys Val Asn Asn Ser Glu Glu Lys Asp Val Pro Lys Met Tyr Cys 235 240 245	774
GGG GCA GAT GGT GAA TGG CTG GTA CCC ATT GGC AAC TGC CTA TGC AAC Gly Ala Asp Gly Glu Trp Leu Val Pro Ile Gly Asn Cys Leu Cys Asn 250 255 260	822
GCT GGG CAT GAG GAG CGG AGC GGA GAA TGC CAA GCT TGC AAA ATT GGA Ala Gly His Glu Glu Arg Ser Gly Glu Cys Gln Ala Cys Lys Ile Gly 265 270 275	870
TAT TAC AAG GCT CTC TCC ACG GAT GCC ACC TGT GCC AAG TGC CCA CCC Tyr Tyr Lys Ala Leu Ser Thr Asp Ala Thr Cys Ala Lys Cys Pro Pro 280 285 290 295	918
CAC AGC TAC TCT GTC TGG GAA GGA GCC ACC TCG TGC ACC TGT GAC CGA His Ser Tyr Ser Val Trp Glu Gly Ala Thr Ser Cys Thr Cys Asp Arg 300 305 310	966
GGC TTT TTC AGA GCT GAC AAC GAT GCT GCC TCT ATG CCC TGC ACC CGT Gly Phe Phe Arg Ala Asp Asn Asp Ala Ala Ser Met Pro Cys Thr Arg 315 320 325	1014
CCA CCA TCT GCT CCC CTG AAC TTG ATT TCA AAT GTC AAC GAG ACA TCT Pro Pro Ser Ala Pro Leu Asn Leu Ile Ser Asn Val Asn Glu Thr Ser 330 335 340	1062
GTG AAC TTG GAA TGG AGT AGC CCT CAG AAT ACA GGT GGC CGC CAG GAC Val Asn Leu Glu Trp Ser Ser Pro Gln Asn Thr Gly Gly Arg Gln Asp 345 350 355	1110
ATT TCC TAT AAT GTG GTA TGC AAG AAA TGT GGA GCT GGT GAC CCC AGC Ile Ser Tyr Asn Val Val Cys Lys Lys Cys Gly Ala Gly Asp Pro Ser 360 365 370 375	1158
AAG TGC CGA CCC TGT GGA AGT GGG GTC CAC TAC ACC CCA CAG CAG AAT Lys Cys Arg Pro Cys Gly Ser Gly Val His Tyr Thr Pro Gln Gln Asn 380 385 390	1206

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FIG. 3C

GGC TTG AAG ACC ACC AAA GTC TCC ATC ACT GAC CTC CTA GCT CAT ACC Gly Leu Lys Thr Thr Lys Val Ser Ile Thr Asp Leu Leu Ala His Thr 395 400 405	1254
AAT TAC ACC TTT GAA ATC TGG GCT GTG AAT GGA GTG TCC AAA TAT AAC Asn Tyr Thr Phe Glu Ile Trp Ala Val Asn Gly Val Ser Lys Tyr Asn 410 415 420	1302
CCT AAC CCA GAC CAA TCA GTT TCT GTC ACT GTG ACC ACC AAC CAA GCA Pro Asn Pro Asp Gln Ser Val Ser Val Thr Val Thr Thr Asn Gln Ala 425 430 435	1350
GCA CCA TCA TCC ATT GCT TTG GTC CAG GCT AAA GAA GTC ACA AGA TAC Ala Pro Ser Ser Ile Ala Leu Val Gln Ala Lys Glu Val Thr Arg Tyr 440 445 450 455	1398
AGT GTG GCA CTG GCT TGG CTG GAA CCA GAT CGG CCC AAT GGG GTA ATC Ser Val Ala Leu Ala Trp Leu Glu Pro Asp Arg Pro Asn Gly Val Ile 460 465 470	1446
CTG GAA TAT GAA GTC AAG TAT TAT GAG AAG GAT CAG AAT GAG CGA AGC Leu Glu Tyr Glu Val Lys Tyr Tyr Glu Lys Asp Gln Asn Glu Arg Ser 475 480 485	1494
TAT CGT ATA GTT CGG ACA GCT GCC AGG AAC ACA GAT ATC AAA GGC CTG Tyr Arg Ile Val Arg Thr Ala Ala Arg Asn Thr Asp Ile Lys Gly Leu 490 495 500	1542
AAC CCT CTC ACT TCC TAT GTT TTC CAC GTG CGA GCC AGG ACA GCA GCT Asn Pro Leu Thr Ser Tyr Val Phe His Val Arg Ala Arg Thr Ala Ala 505 510 515	1590
GGC TAT GGA GAC TTC AGT GAG CCC TTG GAG GTT ACA ACC AAC ACA GTG Gly Tyr Gly Asp Phe Ser Glu Pro Leu Glu Val Thr Thr Asn Thr Val 520 525 530 535	1638
CCT TCC CGG ATC ATT GGA GAT GGG GCT AAC TCC ACA GTC CTT CTG GTC Pro Ser Arg Ile Ile Gly Asp Gly Ala Asn Ser Thr Val Leu Leu Val 540 545 550	1686
TCT GTC TCG GGC AGT GTG GTG CTG GTG GTA ATT CTC ATT GCA GCT TTT Ser Val Ser Gly Ser Val Val Leu Val Val Ile Leu Ile Ala Ala Phe 555 560 565	1734
GTC ATC AGC CGG AGA CGG AGT AAA TAC AGT AAA GCC AAA CAA GAA GCG Val Ile Ser Arg Arg Arg Ser Lys Tyr Ser Lys Ala Lys Gln Glu Ala 570 575 580	1782
GAT GAA GAG AAA CAT TTG AAT CAA GGT GTA AGA ACA TAT GTG GAC CCC Asp Glu Glu Lys His Leu Asn Gln Gly Val Arg Thr Tyr Val Asp Pro 585 590 595	1830

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TTT ACG TAC GAA GAT CCC AAC CAA GCA GTG CGA GAG TTT GCC AAA GAA Phe Thr Tyr Glu Asp Pro Asn Gln Ala Val Arg Glu Phe Ala Lys Glu 600 605 610 615	1878
ATT GAC GCA TCC TGC ATT AAG ATT GAA AAA GTT ATA GGA GTT GGT GAA Ile Asp Ala Ser Cys Ile Lys Ile Glu Lys Val Ile Gly Val Gly Glu 620 625 630	1926
TTT GGT GAG GTA TGC AGT GGG CGT CTC AAA GTG CCT GGC AAG AGA GAG Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Val Pro Gly Lys Arg Glu 635 640 645	1974
ATC TGT GTG GCT ATC AAG ACT CTG AAA GCT GGT TAT ACA GAC AAA CAG Ile Cys Val Ala Ile Lys Thr Leu Lys Ala Gly Tyr Thr Asp Lys Gln 650 655 660	2022
AGG AGA GAC TTC CTG AGT GAG GCC AGC ATC ATG GGA CAG TTT GAC CAT Arg Arg Asp Phe Leu Ser Glu Ala Ser Ile Met Gly Gln Phe Asp His 665 670 675	2070
CCG AAC ATC ATT CAC TTG GAA GGC GTG GTC ACT AAA TGT AAA CCA GTA Pro Asn Ile Ile His Leu Glu Gly Val Val Thr Lys Cys Lys Pro Val 680 685 690 695	2118
ATG ATC ATA ACA GAG TAC ATG GAG AAT GGC TCC TTG GAT GCA TTC CTC Met Ile Ile Thr Glu Tyr Met Glu Asn Gly Ser Leu Asp Ala Phe Leu 700 705 710	2166
AGG AAA AAT GAT GGC AGA TTT ACA GTC ATT CAG CTG GTG GGC ATG CTT Arg Lys Asn Asp Gly Arg Phe Thr Val Ile Gln Leu Val Gly Met Leu 715 720 725	2214
CGT GGC ATT GGG TCT GGG ATG AAG TAT TTA TCT GAT ATG AGC TAT GTG Arg Gly Ile Gly Ser Gly Met Lys Tyr Leu Ser Asp Met Ser Tyr Val 730 735 740	2262
CAT CGT GAT CTG GCC GCA CGG AAC ATC CTG GTG AAC AGC AAC TTG GTC His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val 745 750 755	2310
TGC AAA GTG TCT GAT TTT GGC ATG TCC CGA GTG CTT GAG GAT GAT CCG Cys Lys Val Ser Asp Phe Gly Met Ser Arg Val Leu Glu Asp Asp Pro 760 765 770 775	2358
GAA GCA GCT TAC ACC ACC AGG GGT GGC AAG ATT CCT ATC CGG TGG ACT Glu Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr 780 785 790	2406
GCG CCA GAA GCA ATT GCC TAT CGT AAA TTC ACA TCA GCA AGT GAT GTA Ala Pro Glu Ala Ile Ala Tyr Arg Lys Phe Thr Ser Ala Ser Asp Val 795 800 805	2454

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FIG. 3E

TGG AGC TAT GGA ATC GTT ATG TGG GAA GTG ATG TCG TAC GGG GAG AGG	2502
Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met Ser Tyr Gly Glu Arg	
810 815 820	
CCC TAT TGG GAT ATG TCC AAT CAA GAT GTG ATT AAA GCC ATT GAG GAA	2550
Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile Lys Ala Ile Glu Glu	
825 830 835	
GGC TAT CGG TTA CCC CCT CCA ATG GAC TGC CCC ATT GCG CTC CAC CAG	2598
Gly Tyr Arg Leu Pro Pro Pro Met Asp Cys Pro Ile Ala Leu His Gln	
840 845 850 855	
CTG ATG CTA GAC TGC TGG CAG AAG GAG AGG AGC GAC AGG CCT AAA TTT	2646
Leu Met Leu Asp Cys Trp Gln Lys Glu Arg Ser Asp Arg Pro Lys Phe	
860 865 870	
GGG CAG ATT GTC AAC ATG TTG GAC AAA CTC ATC CGC AAC CCC AAC AGC	2694
Gly Gln Ile Val Asn Met Leu Asp Lys Leu Ile Arg Asn Pro Asn Ser	
875 880 885	
TTG AAG AGG ACA GGG ACG GAG AGC TCC AGA CCT AAC ACT GCC TTG TTG	2742
Leu Lys Arg Thr Gly Thr Glu Ser Ser Arg Pro Asn Thr Ala Leu Leu	
890 895 900	
GAT CCA AGC TCC CCT GAA TTC TCT GCT GTG GTA TCA GTG GGC GAT TGG	2790
Asp Pro Ser Ser Pro Glu Phe Ser Ala Val Val Ser Val Gly Asp Trp	
905 910 915	
CTC CAG GCC ATT AAA ATG GAC CGG TAT AAG GAT AAC TTC ACA GCT GCT	2838
Leu Gln Ala Ile Lys Met Asp Arg Tyr Lys Asp Asn Phe Thr Ala Ala	
920 925 930 935	
GGT TAT ACC ACA CTA GAG GCT GTG GTG CAC GTG AAC CAG GAG GAC CTG	2886
Gly Tyr Thr Thr Leu Glu Ala Val Val His Val Asn Gln Glu Asp Leu	
940 945 950	
GCA AGA ATT GGT ATC ACA GCC ATC ACG CAC CAG AAT AAG ATT TTG AGC	2934
Ala Arg Ile Gly Ile Thr Ala Ile Thr His Gln Asn Lys Ile Leu Ser	
955 960 965	
AGT GTC CAG GCA ATG CGA ACC CAA ATG CAG CAG ATG CAC GGC AGA ATG	2982
Ser Val Gln Ala Met Arg Thr Gln Met Gln Gln Met His Gly Arg Met	
970 975 980	
GTT CCC GTC TGAGCCAGTA CTGAATAAAC TCAAACTCT TGAAATTAGT	3031
Val Pro Val	
985	
TTACCTCATC CATGCACTTT AATTGAAGAA CTGCACTTTT TTTACTTCGT CTTGCCCCTC	3091
TGAAATTAAA GAAATGAAAA AAAAA	3116

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FIG. 4A

CGGTGCGAGC GAACAGGAGT GGGGGGGAAA TTAAAAAAG CTAAACGTGG AGCAGCCGAT	60
CGGGGACCGA GAAGGGGAAT CGATGCAAGG AGCACACTAA AACAAAAGCT ACTTCGGAAC	120
AAACAGCATT TAAAAATCCA CGACTCAAGA TAACTGAAAC CTAAAATAAA ACCTGCTCAT	180
GCACC ATG GTT TTT CAA ACT CGG TAC CCT TCA TGG ATT ATT TTA TGC Met Val Phe Gln Thr Arg Tyr Pro Ser Trp Ile Ile Leu Cys	227
1 5 10	
TAC ATC TGG CTG CTC CGC TTT GCA CAC ACA GGG GAG GCG CAG GCT GCG Tyr Ile Trp Leu Leu Arg Phe Ala His Thr Gly Glu Ala Gln Ala Ala	275
15 20 25 30	
AAG GAA GTA CTA CTG CTG GAT TCT AAA GCA CAA CAA ACA GAG TTG GAG Lys Glu Val Leu Leu Leu Asp Ser Lys Ala Gln Gln Thr Glu Leu Glu	323
35 40 45	
TGG ATT TCC TCT CCA CCC AAT GGG TGG GAA GAA ATT AGT GGT TTG GAT Trp Ile Ser Ser Pro Pro Asn Gly Trp Glu Glu Ile Ser Gly Leu Asp	371
50 55 60	
GAG AAC TAT ACC CCG ATA CGA ACA TAC CAG GTG TGC CAA GTC ATG GAG Glu Asn Tyr Thr Pro Ile Arg Thr Tyr Gln Val Cys Gln Val Met Glu	419
65 70 75	
CCC AAC CAA AAC AAC TGG CTG CGG ACT AAC TGG ATT TCC AAA GGC AAT Pro Asn Gln Asn Asn Trp Leu Arg Thr Asn Trp Ile Ser Lys Gly Asn	467
80 85 90	
GCA CAA AGG ATT TTT GTA GAA TTG AAA TTC ACC CTG AGG GAT TGT AAC Ala Gln Arg Ile Phe Val Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn	515
95 100 105 110	
AGT CTT CCT GGA GTA CTG GGA ACT TGC AAG GAA ACA TTT AAT TTG TAC Ser Leu Pro Gly Val Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr	563
115 120 125	
TAT TAT GAA ACA GAC TAT GAC ACT GGC AGG AAT ATA AGA GAA AAC CTC Tyr Tyr Glu Thr Asp Tyr Asp Thr Gly Arg Asn Ile Arg Glu Asn Leu	611
130 135 140	
TAT GTA AAA ATA GAC ACC ATT GCT GCA GAT GAA AGT TTT ACC CAA GGT Tyr Val Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Gly	659
145 150 155	
GAC CTT GGT GAA AGA AAG ATG AAG CTT AAC ACT GAG GTG AGA GAG ATT Asp Leu Gly Glu Arg Lys Met Lys Leu Asn Thr Glu Val Arg Glu Ile	707
160 165 170	

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FIG. 4B

GGA CCT TTG TCC AAA AAG GGA TTC TAT CTT GCC TTT CAG GAT GTA GGG Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly 175 180 185 190	755
GCT TGC ATA GCT TTG GTT TCT GTC AAA GTG TAC TAC AAG AAG TGC TGG Ala Cys Ile Ala Leu Val Ser Val Lys Val Tyr Tyr Lys Lys Cys Trp 195 200 205	803
TCC ATT ATT GAG AAC TTA GCT ATC TTT CCA GAT ACA GTG ACT GGT TCA Ser Ile Ile Glu Asn Leu Ala Ile Phe Pro Asp Thr Val Thr Gly Ser 210 215 220	851
GAA TTT TCC TCT TTA GTC GAG GTT CGA GGG ACA TGT GTC AGC AGT GCA Glu Phe Ser Ser Leu Val Glu Val Arg Gly Thr Cys Val Ser Ser Ala 225 230 235	899
GAG GAA GAA GCG GAA AAC GCC CCC AGG ATG CAC TGC AGT GCA GAA GGA Glu Glu Glu Ala Glu Asn Ala Pro Arg Met His Cys Ser Ala Glu Gly 240 245 250	947
GAA TGG TTA GTG CCC ATT GGA AAA TGT ATC TGC AAA GCA GGC TAC CAG Glu Trp Leu Val Pro Ile Gly Lys Cys Ile Cys Lys Ala Gly Tyr Gln 255 260 265 270	995
CAA AAA GGA GAC ACT TGT GAA CCC TGT GGC CGT GGG TTC TAC AAG TCT Gln Lys Gly Asp Thr Cys Glu Pro Cys Gly Arg Gly Phe Tyr Lys Ser 275 280 285	1043
TCC TCT CAA GAT CTT CAG TGC TCT CGT TGT CCA ACT CAC AGT TTT TCT Ser Ser Gln Asp Leu Gln Cys Ser Arg Cys Pro Thr His Ser Phe Ser 290 295 300	1091
GAT AAA GAA GGC TCC TCC AGA TGT GAA TGT GAA GAT GGG TAT TAC AGG Asp Lys Glu Gly Ser Ser Arg Cys Glu Cys Glu Asp Gly Tyr Tyr Arg 305 310 315	1139
GCT CCA TCT GAC CCA CCA TAC GTT GCA TGC ACA AGG CCT CCA TCT GCA Ala Pro Ser Asp Pro Pro Tyr Val Ala Cys Thr Arg Pro Pro Ser Ala 320 325 330	1187
CCA CAG AAC CTC ATT TTC AAC ATC AAC CAA ACC ACA GTA AGT TTG GAA Pro Gln Asn Leu Ile Phe Asn Ile Asn Gln Thr Thr Val Ser Leu Glu 335 340 345 350	1235
TGG AGT CCT CCT GCA GAC AAT GGG GGA AGA AAC GAT GTG ACC TAC AGA Trp Ser Pro Pro Ala Asp Asn Gly Gly Arg Asn Asp Val Thr Tyr Arg 355 360 365	1283
ATA TTG TGT AAG CGG TGC AGT TGG GAG CAG GGC GAA TGT GTT CCC TGT Ile Leu Cys Lys Arg Cys Ser Trp Glu Gln Gly Glu Cys Val Pro Cys 370 375 380	1331

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FIG. 4C

GGG AGT AAC ATT GGA TAC ATG CCC CAG CAG ACT GGA TTA GAG GAT AAC Gly Ser Asn Ile Gly Tyr Met Pro Gln Gln Thr Gly Leu Glu Asp Asn 385 390 395	1379
TAT GTC ACT GTC ATG GAC CTG CTA GCC CAC GCT AAT TAT ACT TTT GAA Tyr Val Thr Val Met Asp Leu Leu Ala His Ala Asn Tyr Thr Phe Glu 400 405 410	1427
GTT GAA GCT GTA AAT GGA GTT TCT GAC TTA AGC CGA TCC CAG AGG CTC Val Glu Ala Val Asn Gly Val Ser Asp Leu Ser Arg Ser Gln Arg Leu 415 420 425 430	1475
TTT GCT GCT GTC AGT ATC ACC ACT GGT CAA GCA GCT CCC TCG CAA GTG Phe Ala Ala Val Ser Ile Thr Thr Gly Gln Ala Ala Pro Ser Gln Val 435 440 445	1523
AGC GGA GTA ATG AAG GAG AGA GTA CTG CAG CGG AGT GTC GAG CTT TCC Ser Gly Val Met Lys Glu Arg Val Leu Gln Arg Ser Val Glu Leu Ser 450 455 460	1571
TGG CAG GAA CCA GAG CAT CCC AAT GGA GTC ATC ACA GAA TAT GAA ATC Trp Gln Glu Pro Glu His Pro Asn Gly Val Ile Thr Glu Tyr Glu Ile 465 470 475	1619
AAG TAT TAC GAG AAA GAT CAA AGG GAA CGG ACC TAC TCA ACA GTA AAA Lys Tyr Tyr Glu Lys Asp Gln Arg Glu Arg Thr Tyr Ser Thr Val Lys 480 485 490	1667
ACC AAG TCT ACT TCA GCC TCC ATT AAT AAT CTG AAA CCA GGA ACA GTG Thr Lys Ser Thr Ser Ala Ser Ile Asn Asn Leu Lys Pro Gly Thr Val 495 500 505 510	1715
TAT GTT TTC CAG ATT CGG GCT TTT ACT GCT GCT GGT TAT GGA AAT TAC Tyr Val Phe Gln Ile Arg Ala Phe Thr Ala Ala Gly Tyr Gly Asn Tyr 515 520 525	1763
AGT CCC AGA CTT GAT GTT GCT ACA CTA GAG GAA GCT ACA GGT AAA ATG Ser Pro Arg Leu Asp Val Ala Thr Leu Glu Glu Ala Thr Gly Lys Met 530 535 540	1811
TTT GAA GCT ACA GCT GTC TCC AGT GAA CAG AAT CCT GTT ATT ATC ATT Phe Glu Ala Thr Ala Val Ser Ser Glu Gln Asn Pro Val Ile Ile Ile 545 550 555	1859
GCT GTG GTT GCT GTA GCT GGG ACC ATC ATT TTG GTG TTC ATG GTC TTT Ala Val Val Ala Val Ala Gly Thr Ile Ile Leu Val Phe Met Val Phe 560 565 570	1907
GGC TTC ATC ATT GGG AGA AGG CAC TGT GGT TAT AGC AAA GCT GAC CAA Gly Phe Ile Ile Gly Arg Arg His Cys Gly Tyr Ser Lys Ala Asp Gln 575 580 585 590	1955

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GAA GGC GAT GAA GAG CTT TAC TTT CAT TTT AAA TTT CCA GGC ACC AAA Glu Gly Asp Glu Glu Leu Tyr Phe His Phe Lys Phe Pro Gly Thr Lys 595 600 605	2003
ACC TAC ATT GAC CCT GAA ACC TAT GAG GAC CCA AAT AGA GCT GTC CAT Thr Tyr Ile Asp Pro Glu Thr Tyr Glu Asp Pro Asn Arg Ala Val His 610 615 620	2051
CAA TTC GCC AAG GAG CTA GAT GCC TCC TGT ATT AAA ATT GAG CGT GTG Gln Phe Ala Lys Glu Leu Asp Ala Ser Cys Ile Lys Ile Glu Arg Val 625 630 635	2099
ATT GGT GCA GGA GAA TTC GGT GAA GTC TGC AGT GGC CGT TTG AAA CTT Ile Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Leu 640 645 650	2147
CCA GGG AAA AGA GAT GTT GCA GTA GCC ATA AAA ACC CTG AAA GTT GGT Pro Gly Lys Arg Asp Val Ala Val Ala Ile Lys Thr Leu Lys Val Gly 655 660 665 670	2195
TAC ACA GAA AAA CAA AGG AGA GAC TTT TTG TGT GAA GCA AGC ATC ATG Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Cys Glu Ala Ser Ile Met 675 680 685	2243
GGG CAG TTT GAC CAC CCA AAT GTT GTC CAT TTG GAA GGG GTT GTT ACA Gly Gln Phe Asp His Pro Asn Val Val His Leu Glu Gly Val Val Thr 690 695 700	2291
AGA GGG AAA CCA GTC ATG ATA GTA ATA GAG TTC ATG GAA AAT GGA GCC Arg Gly Lys Pro Val Met Ile Val Ile Glu Phe Met Glu Asn Gly Ala 705 710 715	2339
CTA GAT GCA TTT CTC AGG AAA CAT GAT GGG CAA TTT ACA GTC ATT CAG Leu Asp Ala Phe Leu Arg Lys His Asp Gly Gln Phe Thr Val Ile Gln 720 725 730	2387
TTA GTA GGA ATG CTG AGA GGA ATT GCT GCT GGA ATG AGA TAT TTG GCT Leu Val Gly Met Leu Arg Gly Ile Ala Ala Gly Met Arg Tyr Leu Ala 735 740 745 750	2435
GAT ATG GGA TAT GTT CAC AGG GAC CTT GCA GCT CGC AAT ATT CTT GTC Asp Met Gly Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val 755 760 765	2483
AAC AGC AAT CTC GTT TGT AAA GTG TCA GAT TTT GGC CTG TCC CGA GTT Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val 770 775 780	2531
ATA GAG GAT GAT CCA GAA GCT GTC TAT ACA ACT ACT GGT GGA AAA ATT Ile Glu Asp Asp Pro Glu Ala Val Tyr Thr Thr Thr Gly Gly Lys Ile 785 790 795	2579

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FIG. 4E

CCA	GTA	AGG	TGG	ACA	GCA	CCC	GAA	GCC	ATC	CAG	TAC	CGG	AAA	TTC	ACA	2627
Pro	Val	Arg	Trp	Thr	Ala	Pro	Glu	Ala	Ile	Gln	Tyr	Arg	Lys	Phe	Thr	
800						805					810					
TCA	GCC	AGT	GAT	GTA	TGG	AGC	TAT	GGA	ATA	GTC	ATG	TGG	GAA	GTT	ATG	2675
Ser	Ala	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Ile	Val	Met	Trp	Glu	Val	Met	
815					820					825					830	
TCT	TAT	GGA	GAA	AGA	CCT	TAT	TGG	GAC	ATG	TCA	AAT	CAA	GAT	GTT	ATA	2723
Ser	Tyr	Gly	Glu	Arg	Pro	Tyr	Trp	Asp	Met	Ser	Asn	Gln	Asp	Val	Ile	
				835					840					845		
AAA	GCA	ATA	GAA	GAA	GGT	TAT	CGT	TTA	CCA	GCA	CCC	ATG	GAC	TGC	CCA	2771
Lys	Ala	Ile	Glu	Glu	Gly	Tyr	Arg	Leu	Pro	Ala	Pro	Met	Asp	Cys	Pro	
			850					855					860			
GCT	GGC	CTT	CAC	CAG	CTA	ATG	TTG	GAT	TGT	TGG	CAA	AAG	GAG	CGT	GCT	2819
Ala	Gly	Leu	His	Gln	Leu	Met	Leu	Asp	Cys	Trp	Gln	Lys	Glu	Arg	Ala	
		865					870					875				
GAA	AGG	CCA	AAA	TTT	GAA	CAG	ATA	GTT	GGA	ATT	CTA	GAC	AAA	ATG	ATT	2867
Glu	Arg	Pro	Lys	Phe	Glu	Gln	Ile	Val	Gly	Ile	Leu	Asp	Lys	Met	Ile	
880						885					890					
CGA	AAC	CCA	AAT	AGT	CTG	AAA	ACT	CCC	CTG	GGA	ACT	TGT	AGT	AGG	CCA	2915
Arg	Asn	Pro	Asn	Ser	Leu	Lys	Thr	Pro	Leu	Gly	Thr	Cys	Ser	Arg	Pro	
895					900					905					910	
ATA	AGC	CCT	CTT	CTG	GAT	CAA	AAC	ACT	CCT	GAT	TTC	ACT	ACC	TTT	TGT	2963
Ile	Ser	Pro	Leu	Leu	Asp	Gln	Asn	Thr	Pro	Asp	Phe	Thr	Thr	Phe	Cys	
				915					920					925		
TCA	GTT	GGA	GAA	TGG	CTA	CAA	GCT	ATT	AAG	ATG	GAA	AGA	TAT	AAA	GAT	3011
Ser	Val	Gly	Glu	Trp	Leu	Gln	Ala	Ile	Lys	Met	Glu	Arg	Tyr	Lys	Asp	
			930					935					940			
AAT	TTC	ACG	GCA	GCT	GGC	TAC	AAT	TCC	CTT	GAA	TCA	GTA	GCC	AGG	ATG	3059
Asn	Phe	Thr	Ala	Ala	Gly	Tyr	Asn	Ser	Leu	Glu	Ser	Val	Ala	Arg	Met	
		945					950					955				
ACT	ATT	GAG	GAT	GTG	ATG	AGT	TTA	GGG	ATC	ACA	CTG	GTT	GGT	CAT	CAA	3107
Thr	Ile	Glu	Asp	Val	Met	Ser	Leu	Gly	Ile	Thr	Leu	Val	Gly	His	Gln	
	960					965					970					
AAG	AAA	ATC	ATG	AGC	AGC	ATT	CAG	ACT	ATG	AGA	GCA	CAA	ATG	CTA	CAT	3155
Lys	Lys	Ile	Met	Ser	Ser	Ile	Gln	Thr	Met	Arg	Ala	Gln	Met	Leu	His	
975						980				985					990	
TTA	CAT	GGA	ACT	GGC	ATT	CAA	GTG	TGATATGCAT	TTCTCCCTTT	TAAGGGAGAT						3209
Leu	His	Gly	Thr	Gly	Ile	Gln	Val									
				995												

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FIG. 4F

TACAGACTGC	AAGAGAACAG	TACTGGCCTT	CAGTATATGC	ATAGAATGCT	GCTAGAAGAC	3269
AAGTGATGTC	CTGGGTCCTT	CCAACAGTGA	AGAGAAGATT	TAAGAAGCAC	CTATAGACTT	3329
GAACCTCCTAA	GTGCCACCAG	AATATATAAA	AAGGGAATTT	AGGATCCACC	ATCGGTGGCC	3389
AGGAAAATAG	CAGTGACAAT	AAACAAAGTA	CTACCTGAAA	AACATCCAAA	CACCTTGAGC	3449
TCTCTAACCT	CCTTTTGTGTC	TTATAGACTT	TTTAAAATGT	ACATAAAGAA	TTTAAGAAAG	3509
AATATATTTG	TCAAATAAAA	TCATGATCTT	ATTGTTAAAA	TTAATGAAAT	ATTTTCCTTA	3569
AATATGTGAT	TTCAGACTAT	TCCTTTTTTAA	AATCATTTGT	GTTTATTCTT	CATAAGGACT	3629
TTGTTTTAGA	AAGCTGTTTA	TAGCTTTGGA	CCTTTTGTAGT	GTTAAATCTG	TAACATTACT	3689
ACACTGGGTA	CCTTTGAAAAG	AATCTCAAAT	TTCAAAAGAA	ATAGCATGAT	TGAAGATACA	3749
TCTCTGTTAG	AACATTGGTA	TCCTTTTTTGT	GCCATTTTAT	TCTGTTTAAT	CAGTGCTGTT	3809
TTGATATTGT	TTGCTAATTG	GCAGGTAGTC	AAGAAAATGC	AAGTTGCCAA	GAGCTCTGAT	3869
ATTTTTTAAA	AAGAATTTTT	TTGTAAAGAT	CAGACAACAC	ACTATCTTTT	CAATGAAAAA	3929
AGCAATAATG	ATCCATACAT	ACTATAAGGC	ACTTTTAACA	GATTGTTTAT	AGAGTGATTT	3989
TACTAGAAAG	AATTTAATAA	ACTCGAAGTT	TAGGTTTATG	AGTATATAAA	CAAATGAGGC	4049
ACTTCATCTG	AAGAATGTTG	GTGAAGGCAA	GTCTCTGAAA	GCAGAACTAT	CCAGTGTTAT	4109
CTAAAAATTA	ATCTGAGCAC	ATCAAGATTT	TTTCATTCTC	GTGACATTAG	GAAATTTAGG	4169
ATAAATAGTT	GACATATATT	TTATATCCTC	TTCTGTTGAA	TGCAGTCCAA	ACATGAAAGG	4229
AAATAATTGT	TTTATATTAT	AACTCTGAAG	CATGATAAAG	GGGCAGTTCA	CAATTTTCAC	4289
CATTTAAACA	CAAATTTGCT	GCACAGAATA	TCACCATTCG	AGTTCAAAAC	AAAACAAAAC	4349
AAAAAGTCTT	TTGTTTGTGA	AACTGATGC	AAGAACTTG	TTAAATGAAA	GGACTCTTTA	4409
CCCTAGAAGG	AAGAGGTGAA	GGATCTGGCT	TGTTTTTAAA	GCTTTATTTA	TTAAACCATA	4469
TTATTTGATT	ACTGTGTTAG	AATTCATAA	GCAATAATTA	AATGTGTCTT	TATGGAATTC	4529

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FIG. 5A

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CONS  MARARPP.....s.1l..l1l1dal...aa.pa.EvtLldskt.qgeLgWishPp..Gwee.sg.den.tpirTYqCnvme.sqnn.WLrtnwi:
EPH      MERRWPLGLGLVLLLCAPLPPGARAKEVTIMDTSKAQGELGWLLDPPKDGWSEQQILNGT.PLYMYQDCPMQGRDDTDHWRSLRSNIY
ECK      MELQAAARACFALLWGCALAAAAAQAQKEVLLDFAAAGGELGWLTHPYGKGWDLMONIMDM.PIYMSVCNVMSGDQDN.WLRTNWVY
HEK4     MDCQLSILLLLSCSVLDSFGELIPQPSNEVNLDDSKTIQGELGWISYPH.GWEEISGVDEHYTPRTYQVCNVMDHSQNN.WLRTNWVP
HEK5     LLAAVEETLMDSTTATAELGMMVHPPS.GWEEVSGYDENMNTIRTYQVCNVFESSQNN.WLRTKFIR
HEK7     ALRTLASPSNEVNLDSRTVMGDLGWIAFPKN.GWEEIGEVDENYAPIHTYQVCVKMEQNQNN.WLLTSWIS
HEK8     MAGIFYFALFSCLFGICDAVTGSRVYPANEVTLLDSRSVQGELGWIASPLEGGWEEVSIMDEKNTPIRTYQVCNVMEPSQNN.WLRTDWIT
HEK2     MARARPPPPPPGLLPLPLPLPLLLPAGCRALHEETLMDTKWTSSELAWTSHPS.GWEEVSGYDEAMNPRTYQVCNVRESSQNN.WLRTGFIW
HEK11    MVFQTRYPSWIIILCYIWLRLFAHTGEAQAKEVLLDLSKAQOTELEWISSPPN.GWEEISGLDENYTPRTYQVCQVMEPNQNN.WLRTNWIIS
          *
          *
CONS  rg.gaqriyvElkFt.RDCnS.Pgvlgt..CKETFNlyyEsDdd....tgrniren.fvKidTiAaDesftq.Dlgdr.mklNtevrsvGplskkGfYL
EPH    RGEASRVHVELQFTVRDCKSFPGGAGPLGCKETFNLLYMESDQD....VGIQLRRPLFQKVTTVAADQSFTIRDLASGSVKLNVERCSLGRLTRRGLYL
ECK    RG.EAERNNFELNFTVRDCNSFPGGASS..CKETFNLYYAESDLD....YGTNFQKRLFTKIDTIAPEITVSSDFAEHVKLNVEERSVGPLTRKGFYL
HEK4   RN.SAQKIYVELKFTLRDCNSIPLVLGT..CKETFNLYYMESDDD....HGKVFREHQFTKIDTIAADESFTQMDLGDRLKLANTEIREVGPVKKGFYL
HEK5   RR.GAHRHIVEMKFSVRDCSSIPSVPGS..CKETFNLYYEADFSATKTFPNMNMENPVKVDITIAADESFSQVLDGGRVMKINTEVRSFGPVSRSGFYL
HEK7   NE.GASRIFIELKFTLRDCNSLPGGLGT..CKETFNMYFESDDQ....NGRNIKENQYIKIDTIAADESFTELDGDVRMVKLANTEIRDVGPLSKKGFYL
HEK8   RE.GAQRVYIEIKFTLRDCNSLPGVMGT..CKETFNLYYVESDND....KERFIRENQYKIDTIAADESFTQVDIGDRIMKLANTEIRDVGPLSKKGFYL
HEK2   RR.DVQRVYVELKFTVRDCNSIPNIPGS..CKETFNLFYFEADSDVASASSPFWMENPVKVDITIAPEDESFSRLDAGR....NTKVRSGPPLSKAGFYL
HEK11  KG.NAQRIFVELKFTLRDCNSLPGVLGT..CKETFNLYYETDYD....TGRNIRENLVVKIDTIAADESFTQDGLGERKMKLANTEVREIGPLSQKGFYL

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FIG. 5B

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*      *      *      *      *      *
CONS  AFqdvGaC.aLvsVrv.ykkCpstv.nIA.Fpdt.tgadssslvevrG.Cvna.....e...pp.m.CsadGEWlVPigkC.CkaGyee...gtaCqaCp
EPH    AFHNPgACVALSVRVFYQRCPETLNGLAQFPDTPG.PA.GLVEVAGTCLPHARASPRPSGAPRMHCSPDGEWLVPGRCHCEPGVEEGSGEACVACP
ECK    AFQDIGACVALLSVRVYKKCPPELLQGLAHFPETIAGSDAPSLATVAGTCVDHA.WPPGGEPRMHCAVDGEWLVPIGQCLQAGYEKVED..ACQACS
HEK4   AFQDVGACVALSVRVYKKCPFTVKNLAMFPDTPV.MDSQSLVEVRGSCVNNS....KEEDPPRMVCSTEGEWLVPIGKCSNAGYEER..GFMCQACR
HEK5   AFQDYGGCMSLIAVRVYRKCPRIIQNGAIFOETLSGAESTSLVAARGSCIANA...EEDVPIKLYCNGDGEWLVPIGRCMCKAGFEAVENGTVCRGCP
HEK7   AFQDVGACIALSVRVYKKCPVVRHLAVFPDTPITGADSSQLLEVSGSCVNHS....VTDEPPKMHCsAEGEWLVPIGKCMCKAGYEER..NGT.CQVCR
HEK8   AFQDVGACIALSVRVYKKCPPLTVRNLAQFPDTPITGADTSSLVEVRGSCVNNS....EEKDVPKMYCGADGEWLVPIGNCLCNAGHEER..SGECQACK
HEK2   AFQDQGACMSLISVRAFVYKKCASTTAGFALFPETLTGAEPSTSLVIAPGTCIPNA...VEVSVPLKLYCNGDGEWLVPIGACTCATGHEPAAKESQCRPCP
HEK11  AFQDVGACIALSVKVYKKCWSIIENLAIFPDVTVTGSEFSSLVEVRGTCVSSA..EEEAENAPRMHCsAEGEWLVPIGKCIKAGYQK..GDTCEPCG
*      *      *      *      *      *
CONS  pgfyka...gd.pClkCpPhs.ttsegatsCtCengy.RadsppsmactTpPsAPrnlisnvnetsv.LewspPadtGgr.Dv.yn.iCkKcg.ga...g
EPH    SGSYRMDMDTPHCLTCPOQSTAESEGATICTCESGHYRAPGEGPOVACTGPPSAPRNLSFSASGTQLSLRWEPPADTGGRQDVRYSVRCSQCQQTADGG
ECK    PGFFKFEASESPCLEPHTLPSPEGATSCCECEGFFRAPQDPASMPCTRPSPAPHYLTAVGMGAKVELRWTPPQDSGGREDIVYSVTCEQCWPES...G
HEK4   PGFYKALDGNMKCAKCPPHSSSTQEDGSMNRCENNIFRADKDPSPMACTRPSPSPRNVISNINETSVIDWSWPLDTGGRKDVTFNIICKKGWNI...K
HEK5   SGTFFKANQGEACTHCPINSRTTSEGATNCVCRNGVYRADLDPLDMPCTTIPSAQAVISSVNETSLMLEWTPPRDSGGREDLVNICKSCGSR...G
HEK7   PGFFKASPHIQSCGKCPPHSYTHEEASTSCVCEKDVFRESDDPTMACTRPSPAPRNAISNVNETSVFLEWIPADTGGKRDVSYIACKKCNSHA...G
HEK8   IGYKALSTDATCAKCPPHSYVMEGATSCCTDRGFFRADNDAAAMPCTRPSPAPLNLSNVNETSVNLEWSSPQNTGGRODISNVVCKKCGAGD..PS
HEK2   PGSYKAKQGEPCPLCPPNSRTTSPAASICTCHNMFYRADSDSADACTTVPSPPRGVISNVNETSLILEWSEPRDLGVRDDLNVNICKK.HGAGGAS
HEK11  RGFYKSSQDLQCSRCPTHFSFDSKESRCECEDGYRAPSPDPVYACTRPSPAPQNLIFNINQTTVSLWSPPADNGGRNDVTYRILCKRCSWEQ...G

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FIG. 5C

* *

CONS .CepCg.nvry.prglgt.t.vtvsdllahtnYtFe.eAvNGVs.1....sp.q.asvsv.ittnqaaps.v.tvr....sr.s.slsW.qep.rpngv
 EPH PCQPCGVGHFSPGARALTTPAVHNGLEPYANYTFNVEAQNGVSLGSSGHAS..TSVISMGHAESLS..GLSLRLVKKEPRQLELTWAGSRPRSPGA
 ECK ECGPCEASVRYSEPPHGLTRTSVTVSDLEPHMNYTFTVEARNGVSLVTSRFR.TASVS..I..NQ...TEPPKVRLEGRSTLSVSW.SIPPPQQR
 HEK4 QCEPCSPNVRF.LPRQFGLTNTTVTTDLLAHTNYTFEIDA VNGVSEL..SSPPRQFAV..SITTNQAAPSPVLTIKKDRTSRNSISLSW.QEPEHPNGI
 HEK5 ACTRCGDNVQYAPRQLGLTEPRIYISDLLAHTQYTFEIQAVNGVTD..QSPFSPQFASV..NITTNQAAPSAVSIMHQVSRVTVDSTITLSW.SQPDQPNGV
 HEK7 VCEECGGHVRYL.PRQSGLKNTSVMVVDLLAHTNYTFEIEAVNGVSDL....SPGARQYVSVNVTTNQAAPSPVTNVKKGIAKNISISLSW.QEEDRPNGI
 HEK8 KCRPCGSGVHYTPQQNGLKTKKVSITDLLAHTNYTFEIWA VNGVSK....YNPNDDQSVSVTVTTNQAAPSSIALVQAKEVTRYSVALLAW.LEPDRPNGV
 HEK2 ACSRCDDNVEFVPRQLGLSEPRVHTSHLLAHTRYTFEVOAVNGVSGK....SPLPPRYAAVNITTNQAAPSEVPTLRHLHSSCGSSLTLSW.APPERPNGV
 HEK11 ECVPCGSNIGMPQQTGLEDNVYVTVMDDLLAHANYTFEVEAVNGVSDL....SRSQRLFAAVSITTGQAAPSQVSGVMKERVLRQSVELS.W.QEPEHPNGV

CONS il.YEvkyekdq.ersy.iv.k.tsvt.dgLkpdT.YvfqvrarTaaGyG..Sr..efef.pea.sgsG...ivvvivs.aga...llvv..v.l..r
 EPH NLTYE...LHVLNQDEERYQMVLEPRVLLTELQPDTTYIVRVRMLTPLGPGFSPDHEFRTPPVSRGLTGCGEIVAVIFGLLLGAALLLGLVFRSRA
 ECK VWKYE.V.TYRKKGDSNSYNVRRTEGFSVTLDDLAPDTTYLVQVQALTQEGQAGSKVHEFQTLSPGSGNLAVIGGVAVGVVLLLVLAGVGVFFIHRRRKN
 HEK4 ILDYE.VKYKQEQETS.YTILRAGTNVTISSLKPDITYVLQIRARTAAGYGTNSRKFEFETSPDFSISGESSQVWMIASAAVAIILLTVVIVVLIGR
 HEK5 ILDYLQYKEKELSEYNATAIKSPNTNTVTVQGLKAGAIYVFQVRARTVAGYGRYSGKMYFQTMTEAEYQTSIQEKPLIIGSSAAGLVFLIAVVVIAIVC
 HEK7 ILEYEIKHFEDQETS.YTII.KSKETTITAEGKLPASVYVFQIRARTAAGYGVFSRRFEFETTPVFAASSDQSQIPVIAVSVTGVILLAVVIGVLLSGR
 HEK8 ILEYEVKYKQDNERSYRIVRTAARNTDIKGLNPLTSYVFHVHRTAAGYGVDFSEPLEVTNTVPSRIIGDCANSTVLLVSVSGSVVLLVILLIAAFVIS
 HEK2 ILDYE.MKYFEK..SEGIASVTQSOMNSVOLDLRDPDARYVWQVRARTVAGYGYQYSRPAEFETTSERGSQAQQLQEQPLIVGSATAGLVFVAVVIAIV
 HEK11 ITEYEIKYKQDNERTYSTVTKTSTASINNLKPGTVVVFQIRAFATAAGYGNYSRPLDVATLEEATGKMFEATAVSSEONPVIIIAVAVVAGTIIILVFM

FIG. 5D

8

CONS .r..qsr.dd.ey.keq.....klpg.ktyidp.TyedPngav.efakeidascikiekviGaGEFGEVcsGrLklp.gkre..VAIKTLKvgy
 EPH QRQRQRHVTAAPPMMWERTSCAELCGTSRHTLHREPWTL..PGWSNFPSRELDPAWLMDVTVICEGEFGEVYRGTLRLPS.QDCKTVAIKTLKDTs
 ECK QRARQSPEDVYFSKSEQ.....LKPLKTYVDPHTYEDPNQAVLKFTTEIHPSCVTRQKVIGAGEFGEVYKGMKLTSSGKKEVPVAIKTLKAGY
 HEK4 FCGYKSKHGADKRLHFGNG.....HLKLPGLRTYVDPHTYEDPTQAVHEFAKELDATNISIDKVVGAGEFGEVCSGRLKLP.S.KKEISVAIKTLKVGy
 HEK5 NRRGFERADSEYTDKLQHYT.....SGHITPGMKIYIDPFTYEDPNEAVREFAKEIDISCVKIEQVIGAGEFGEVCSGHLKLP.GKREIFVAIKTLKSGY
 HEK7 RCGYSKAKQDPEEEKMHFN.....GHIKLPGVRTYIDPHTYEDPNQAVHEFAKEIEASCITTIERVIGAGEFGEVCSGRLKLP.GKRELPVAIKTLKVGy
 HEK8 RRRSKYSKAKQEADEEKHLN.....QGVRTYVDPFTYEDPNQAVREFAKEIDASCIEKVIKGVGEFGEVCSGRLKVP.GKREICVAIKTLKAGY
 HEK2 CLRKQRHGSDEYTEKLQY.....IAPGMKVYIDPFTYEDPNEAVREFAKEIDVSCVKIEEVIGAGEFGEVCSGRLKQP.GRREVFVAIKTLKVGy
 HEK11 VFGFIIGRRHCGYTKADQEGDEELYHFHFKFPGTCTYIDPETYEDPNRAVHQFAKELDASCIEKIERVIGAGEFGEVCSGRLKLP.GKRDVAVAIKTLKVGy

tekQrrdFL.EASIMGQFdHpniihLEGVvtkskPvMiite.MENG.Ld.FLrkdngqftviQLVgMLrGlaaGmKYLsdmYVHRDLAARNILVNSNLV
 EPH PGGQWNNFLREATIMGQFSHPHILHLEGVVTKRKPIMIITEFMENAAALDAFLREREDQLVPGQLVAMLQGIASGMNYSNHNVYHRDLAARNILVNQNLc
 ECK TEKQrVDfLGEAGIMGQFSHhNIrLEGVISKYKPMMIITEYMENGALDKFLREKDGESVLQVLGMLRGIAAGMKYLANMNYVHRDLAARNILVNSNLV
 HEK4 TEKQRRDfLGEASIMGQFDHPNIrLEGVVTKSKPVMIVTEYMENGSLDSFLRKHDAQFTVIQLVGMRLRGIASGMKYLSDMGYVHRDLAARNILINSNLV
 HEK5 TEKQRRDfLSEASIMGQFDHPNVihLEGVVTKSTPVMIIITEFMENGSLDSFLRQNDGQFTVIQLVGMRLRGIAAGMKYLA DMNYVHRDLAARNILVNSNLV
 HEK7 TEKQRRDfLGEASIMGQFDHPNIihLEGVVTKSKPVMIVTEYMENGSLDTFLKNDGQFTVIQLVGMRLRGISAGMKYLSDMGYVHRDLAARNILINSNLV
 HEK8 TDKQRRDfLSEASIMGQFDHPNIihLEGVVTKCPVMIIITEYMENGSLDAFLRKNDGRFTVIQLVGMRLRGISAGMKYLSDMGYVHRDLAARNILVNSNLV
 HEK2 TEQRRDfLSEASIMGQFDHPNIrLEGVVTKSRPVMILTEFMENCALDSFLRLNDGQFTVIQLVGMRLRGIAAGMKYLSMNTYVHRDLAARNILVNSNLV
 HEK11 TEQRRDfLSEASIMGQFDHPNVVhLEGVVTRGKPMIVIEFMENGALHAFLRKHGQFTVIQLVGMRLRGIAAGMRYLADMGYVHRDLAARNILVNSNLV

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FIG. 5E

*
 CONS CKVSDFGLSRVLEDD.pea.yt.trGGKiPIRWTaPEAIayrkFTsASDVWSyGIVmWEVmsyGerPyw.msNqdVikaieegyRLPpPmDCPaal.qLM
 EPH CKVSDFGLTRLL.DDFDGTyET..QGGKiPIRWTaPEAIAHRIFTTASDVWSFGIVMWEVLSFGDKPYGEMSNQEVMSIEDGYRLPPFVDCPAPLYELM
 ECK CKVSDFGLSRVLEDD.PEATyT.TSGGKiPIRWTaPEAIsYrkFTsASDVWSFGIVMWEVMyGERPyWELSNHEVMKAINDGFRLLPTPMDPCPSAIYQLM
 HEK4 CKVSDFGLSRVLEDD.PEAAYT.TRGGKiPIRWTsPEAIAyRKFTsASDVWSyGIVLWEVMSYGERPyWEMSNQDVikaVDEGYRLPPPMDCPaALYQLM
 HEK5 CKVSDFGLSRFLEDDTSDPTyTSALGKFPiRWTaPEAIQYrkFTsASDVWSyGIVMWEVMSYGERPyWDMTNQDVinaIEQDYRLPPPMDCPSALHQLM
 HEK7 CKVSDFGLSRVLEDD.PEAAYT.TRGGKiPIRWTaPEAIAFRKFTsASDVWSyGIVMWEVMSYGERPyWEMTNQDVikaVEEGYRLPSPMDCPaALYQLM
 HEK8 CKVSDFGMSRVLEDD.PEAAYT.TRGGKiPIRWTaPEAIAyRKFTsASDVWSyGIVMWEVMSYGERPyWDMSNQDVikaIEEGYRLPPPMDCPIALHQLM
 HEK2 CKVSDFGLSRFLEDDPSDPTyTSSLGKiPIRWTaPEAIAyRKFTsASDVWSyGIVMWEVMSYGERPyWDMSNQDVinaVEQDYRLPPPMDCPTALHQLM
 HEK11 CKVSDFGLSRVLEDD.PEAAYT.TTGGKiPVRWTaPEAIQYrkFTsASDVWSyGIVMWEVMSYGERPyWDMSNQDVikaIEEGYRLPAPMDCPaGLHQLM

*

CONS ldcWqk.RnrRPkF.qivniLdklirnpnSLktia.assr.s.plld.sgpd.ttfrtvgeWLeaikmgryke.Ftaagyts..avaqmtaeDl.rigvt
 EPH KNCWAYDRARRPHFQKLQAHLEQLLANPHSLRTIANFDPRVTLRLPSLSGSDGIPYRTVSEWLESIRMKRYILHFHSAGLDTMECVLELTAEDLTQMGIT
 ECK MQCWOQERARRPKFADIVSILDKLIRAPDSLKTLaDEFDPVRSIRLPSTSGSEGVPFRVSEWLESIKMQQYTEHFMAAGYTAIEKVVMQMTNDDIKRIGVR
 HEK4 LDCWQKDRNNRPKFEQIVSILDKLIRNPGSLKIITSAARPSNLLLDQSNVDISTFRITGMDLNGVRTAHCKEIFTGVEYSSCDTIAKISTDDMKKVGVT
 HEK5 LDCWQKDRNHRPKFGQIVNTLDKMRNPNSLKAMAPLSSGINPLLDRTIPDYTSFNTVDENLEAIKMGQYKESFANAGTSDVVSQMMEDILRVGVT
 HEK7 LDCWQKERNRPKFEQIVNMLDKLIRNPSSLKTLVNASCRVSNLLAEHSPGSAVRSVGENLEAIKMGRYTEIFMENGYSMDAVAQVLTLEDLRLRGVT
 HEK8 LDCWQKERSDRPKFGQIVNMLDKLIRNPNSLKRGTGTESSRPNTALLDPSSPEFSAVSVGDMWLOAIKMDRYKDNFTAAGYTTLEAVVHVNQEDLARIGIT
 HEK2 LDCWVRDRNLRPKFSQIVNTLDKLRNAASLKVIAAQSGMSQPLLDRTVPDYTTFTTGVDMWLDKAIKMGRYKESFVSAGFASFDLVAQMTAEDLLRIGVT
 HEK11 LDCWQKERAERPKEQIVGILDKMRNPNSLKTPLGTCSRPISPLLDQNTPDFTTFCVSGEWLQAIKMERYKDNFTAAAGNSLESVARMTIEDVMSLGIT

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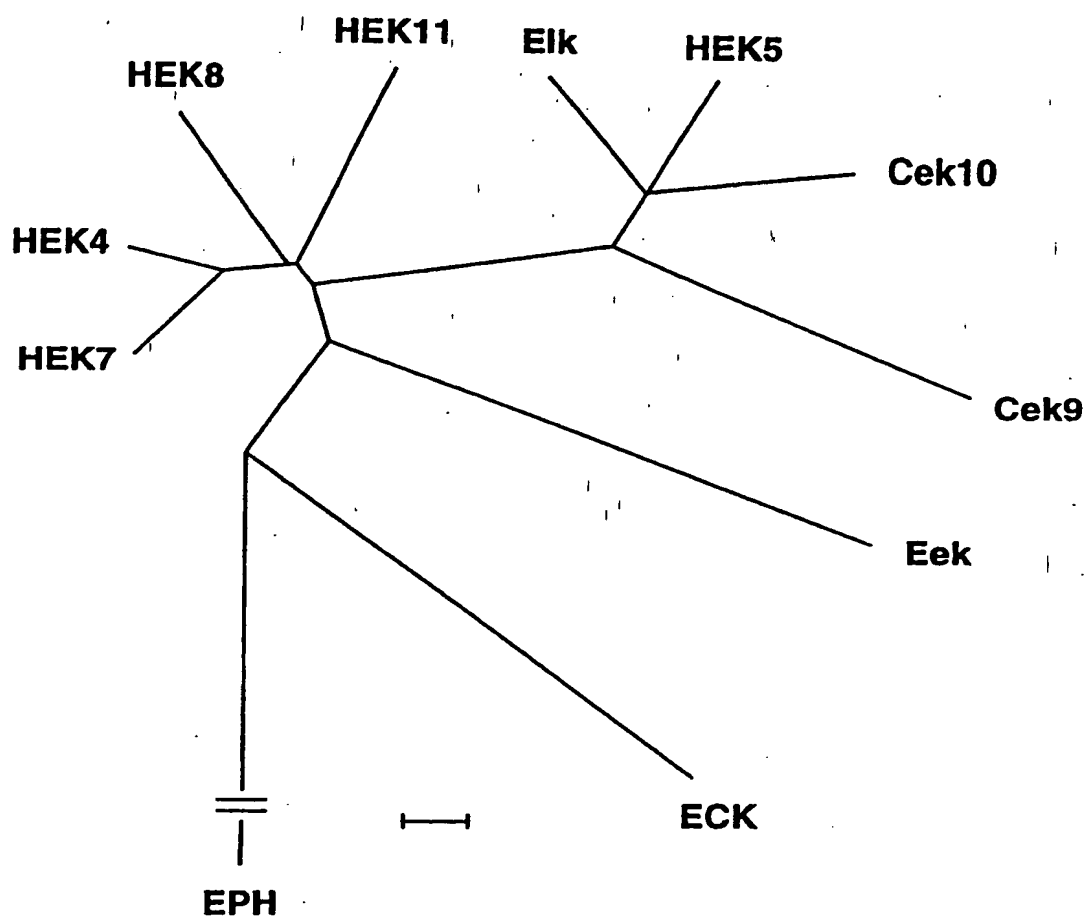
FIG. 5F

CONS	lvghQkkIlSsiq.mr.Qmnggh.p.v.v
EPH	LPGHQKRILCSIQGFKD
ECK	LPGHQKRIAYSLLGLKBDQVNTVGIPI
HEK4	VVGPQKKIISSIKALETOSKNGPVPV
HEK5	LACHQKKILNSIQVMRAQMNQIQSVEV
HEK7	LVGHQKKIMNSLOEMKVQLVNGMVPL
HEK8	AITHQNKILSSVQAMRTQMOMHGRMPV
HEK2	LACHQKKILSSIQDMRLQMNQTLPVQV
HEK11	LVGHQKKIMSSIQTMTRAQMLHLHGTGIQV

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FIG. 6



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FIG. 7A

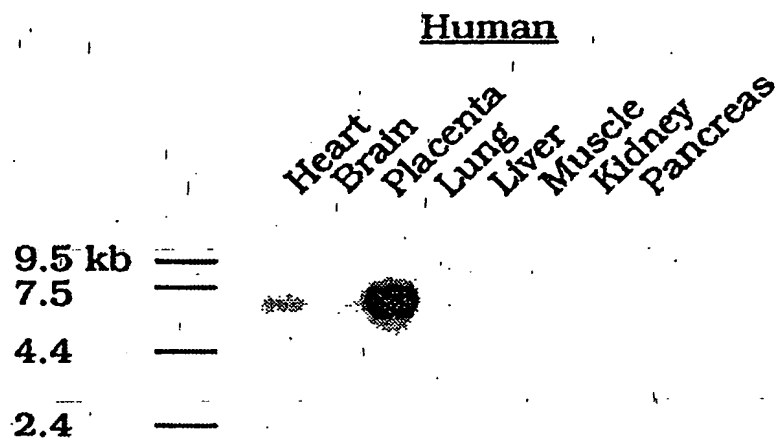
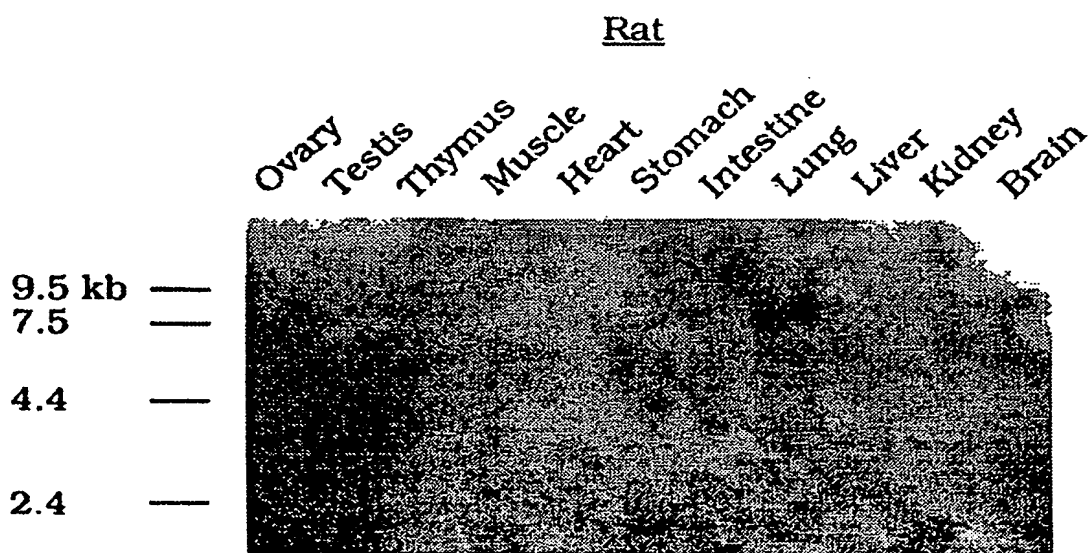


FIG. 7B



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FIG. 8A

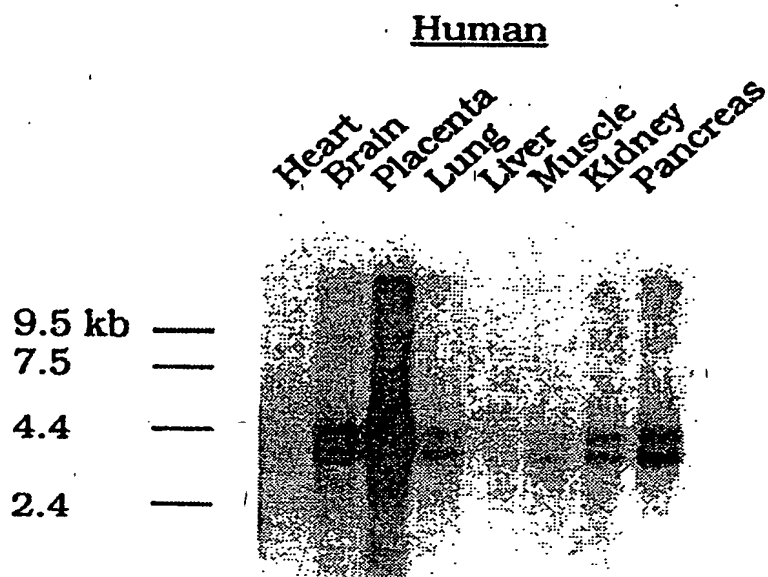
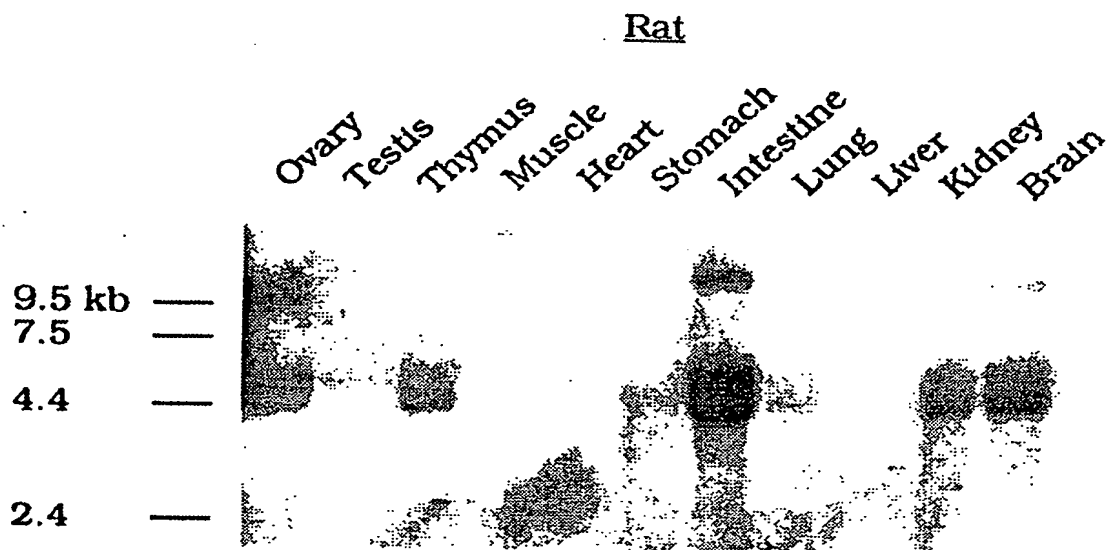


FIG. 8B



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FIG. 9A

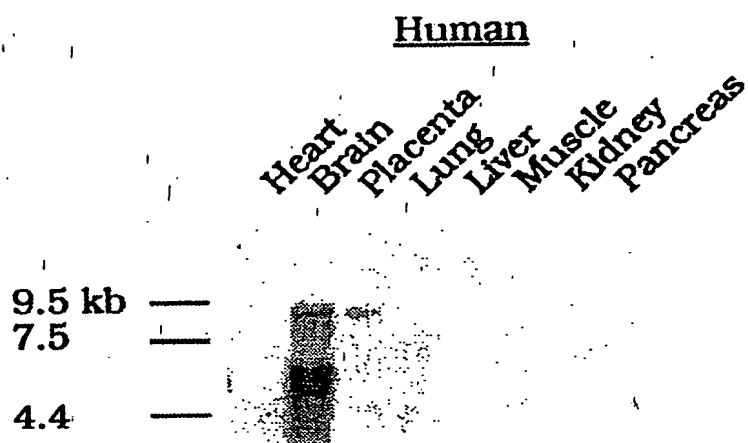
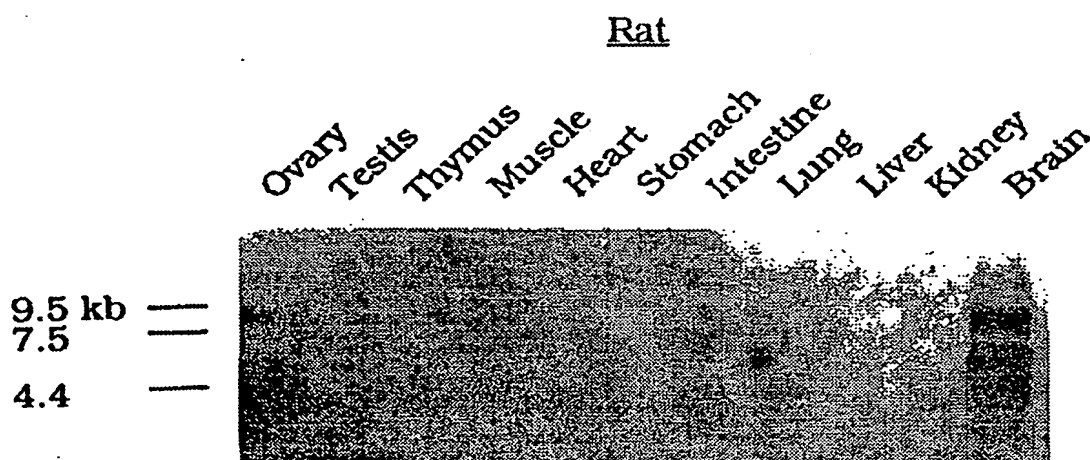


FIG. 9B



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FIG. 10A

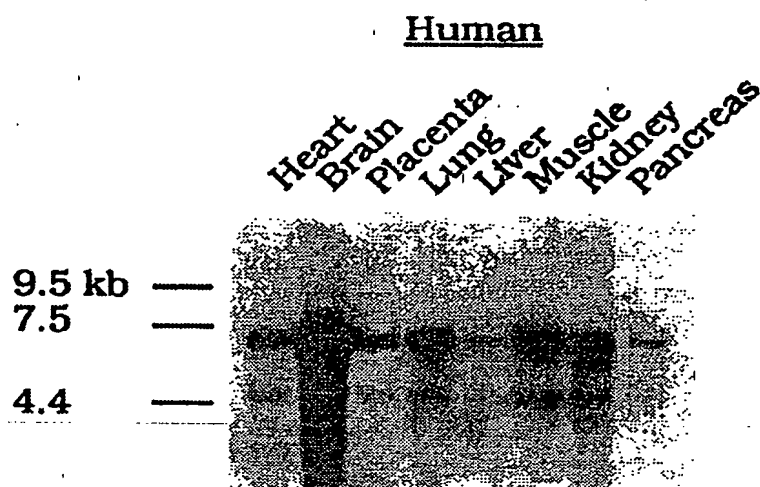
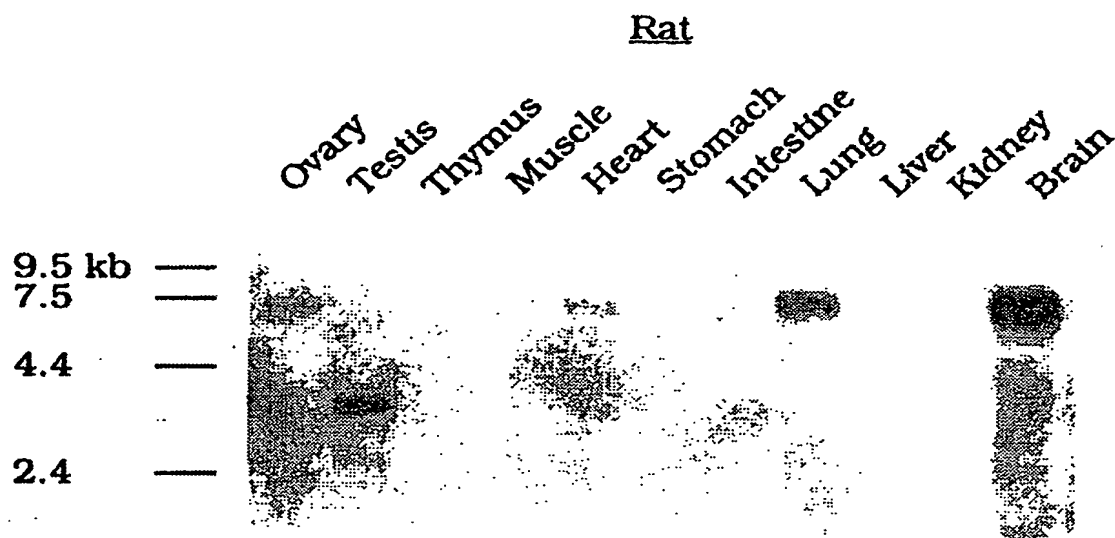


FIG. 10B



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FIG. IIA

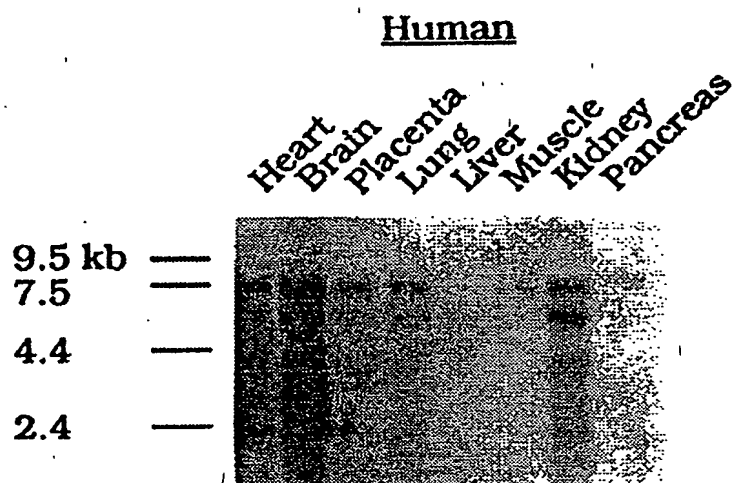
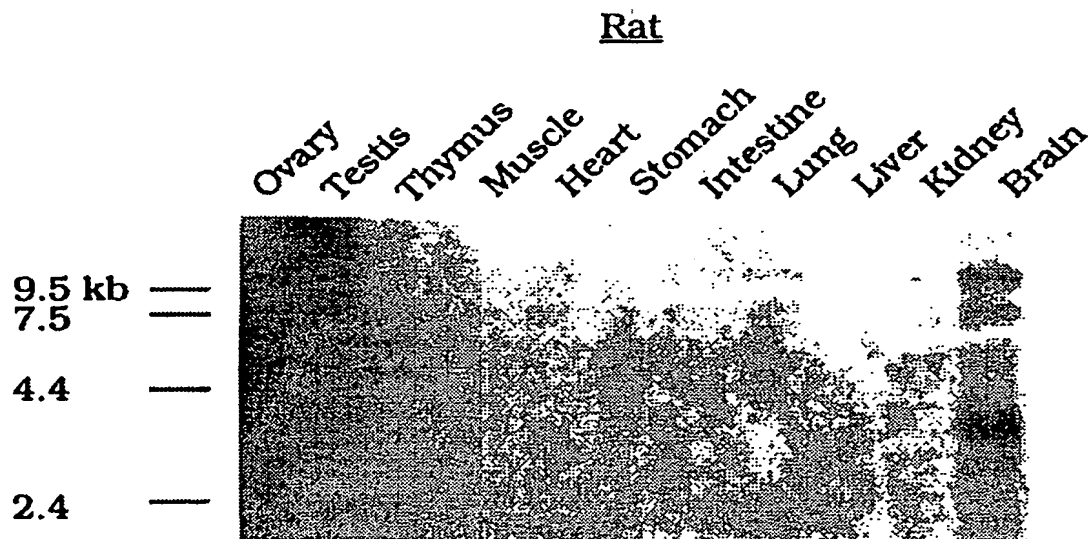


FIG. IIB



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INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/US 95/04681

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/71 C07K16/28 A61K38/17 A61K39/395
C12N15/62 G01N33/566

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO-A-93 00425 (INST MEDICAL W & E HALL) 7 January 1993 see the whole document ----	1-8, 10, 15-18, 20, 23, 25-32, 34
X	DE-A-42 33 782 (CHEMOTHERAPEUTISCHES FORSCHUNG) 14 April 1994 see the whole document ----	1-9, 15-19, 23, 25-32, 34
X	CA-A-2 083 521 (MOUNT SINAI HOSPITAL CORP) 1 October 1993 see the whole document ----- -/--	1-7, 13, 15-18, 23-32, 34

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "Z" document member of the same patent family

Date of the actual completion of the international search

6 September 1995

Date of mailing of the international search report

15. 09. 95

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Authorized officer

Nauche, S

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/US 95/04681

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ONCOGENE, vol. 7, no. 12, December 1992 pages 2499-2506, HEBENSTREIT-GILARDI, P. ET AL.; 'An Eph-related receptor tyrosine kinase gene segmentally expressed in the developing mouse hindbrain.' see the whole document ---	1-8, 11, 15-18, 21, 23, 25-27, 34
X	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 194, 1993 ORLANDO, FL US, pages 698-705, IWASE T., TANAKA M., SUZUKI M., NAITO Y., SUGIMURA H.; 'Identification of protein-tyrosine kinase genes preferentially expressed in embryo stomach and gastric cancer' see the whole document ---	1-9, 15-19, 23, 25-27, 32, 34
X	CELL REGULATION, vol. 2, July 1991 pages 523-534, PASQUALE, E.B.; 'Identification of chicken embryo kinase 5, a developmentally regulated receptor-type tyrosine kinase of the Eph family' see the whole document ---	1-9, 15-19, 23, 25-29, 32, 34
X	ONCOGENE, vol. 8, 1993 pages 1807-1813, SAJJADI F.G., PASQUALE E.B.; 'Five novel avian Eph-related tyrosine kinases are differentially expressed' see the whole document ---	1-11, 15-21, 23, 25-27, 32, 34
X	BRITISH JOURNAL OF CANCER, vol. 69, no. 3, March 1994 pages 417-421, TUZI NL; GULLICK WJ; 'eph, the largest known family of putative growth factor receptors.' see the whole document ---	1-11, 13-21, 23-27, 32, 34
X	ONCOGENE, vol. 8, no. 12, December 1993 pages 3277-3288, MAISONPIERRE PC; BARREZUETA NX; YANCOPOULOS GD; 'Ehk-1 and Ehk-2: two novel members of the Eph receptor-like tyrosine kinase family with distinctive structures and neuronal expression.' cited in the application see the whole document ---	1-8, 10, 15-18, 20, 23, 25-27, 32, 34

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/04681

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ONCOGENE, vol. 6, no. 6, 1991 pages 1057-1061, CHAN, J.; WATT, V.M.; 'eek and erk, new members of the eph subclass of receptor protein-tyrosine kinases' cited in the application see the whole document ---	1-9, 15-18, 23, 25-27, 32,34
X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 89, no. 5, 1 March 1992 WASHINGTON US, pages 1611-1615, WICKS IP;WILKINSON D;SALVARIS E;BOYD AW; 'Molecular cloning of HEK, the gene encoding a receptor tyrosine kinase expressed by human lymphoid tumor cell lines.' cited in the application see the whole document ---	1-8,12, 15-18, 22-27, 32,34
P,X	ONCOGENE, vol. 10, no. 5, 2 March/1995 pages 897-905, FOX GM;HOLST PL;CHUTE HT;LINDBERG RA;JANSSEN AM;BASU R;WELCHER AA; 'cDNA cloning and tissue distribution of five human eph-like receptor protein-tyrosine kinases' see the whole document -----	1-34

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 95/ 04681

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 32
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 32 is directed to a method of treatment of the human/animal body (Rule 39.1(iv)) PCT), the search has been carried out and based on the alleged effects of the compound/ composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/04681

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9300425	07-01-93	AU-B- 655299 EP-A- 0590030 JP-T- 6508747	15-12-94 06-04-94 06-10-94
DE-A-4233782	14-04-94	NONE	
CA-A-2083521		NONE	